ATTACHMENT 2

[redacted]

ATTACHMENT 2 (112 PAGE

5725873

5725873

Class	ISSUE CLASS
424	

UTILITY SERIAL NUMBER	PATENT DATE	PATENT NUMBER
08/684785	MAR 10 1998	

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
08/684,785	07/22/96	424	442	1816	738 VanderVegt

APPLICANTS: MARK E. COOK, MADISON, WI; DARIA L. JEROME, MIDDLETON, WI.

CONTINUING DATA*******
VERIFIED
NONE

ATTACHMENT 2

FOREIGN/PCT APPLICATIONS********
VERIFIED
NONE

FOREIGN FILING LICENSE GRANTED 09/09/96

Foreign priority claimed / 35 USC 119 conditions met	Verified and Acknowledged	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDER CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
☐ yes ☒ no / ☐ yes ☐ no	Examiner's initials	→	WI	0	8	2	$750.00	960296.94011

ADDRESS:
THAD F KRYSHAK
QUARLES & BRADY
411 EAST WISCONSIN AVE
MILWAUKEE WI 53202-4497

TITLE: METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN

U.S. DEPT. OF COMM./ PAT. & TM—PTO-436L (Rev.12-94)

PARTS OF APPLICATION FILED SEPARATELY

Glenda Conditions Examiner

NOTICE OF ALLOWANCE MAILED		CLAIMS ALLOWED	
11-12-97	F. Pierre VanderVegt, Assistant Examiner	Total Claims: 1	Print Claim: 1

ISSUE FEE		DRAWING		
Amount Due	Date Paid	Sheets Drwg.	Figs. Drwg.	Print Fig.
$1320.00	12/4/97 MA	0	0	NONE

David A. Saunders
DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT 182 1816
Primary Examiner

ISSUE BATCH NUMBER: 407

Label Area

PREPARED FOR ISSUE

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

Form PTO-436A (Rev. 8/92)

ISSUE FEE IN FILE

ATACHMENT 2 (112 PAGES)

(FACE)

08/684785

BRIEFED IN [illegible]

PATENT APPLICATION

08684785

APPROVED FOR LICENSE

AUG 2 8 96 26

INITIALS

CONTENTS

Date Entered or Counted			Date Received or Mailed
	1.	Application papers.	
	2.	IDS	10/7/96
	3.	Rej 3mo	02/18/97
	4.	[illegible] (3mos)	6/9/97
	5.	Amdt A	6/9/97
	6.	Decl.	6/9/97
	7.	Final Rej 3mo	10-1-97
	8.	Suppl IDS	9-12-97
	9.	Amdt B (NE)	11/3/97
	10.	Ltr allowability	11-12-97
	11.	PTO Grant MAR 10 1998	
	12.		
	13.		
	14.		
	15.		
	16.		
	17.		
	18.		
	19.		
	20.		
	21.		
	22.		
	23.		
	24.		
	25.		
	26.		
	27.		
	28.		
	29.		
	30.		
	31.		
	32.		

(FRONT)

U.S. GOVERNMENT PRINTING OFFICE: 1996-410-719

PATENT NUMBER

APPLICATION SERIAL NUMBER
08/684,785

APPLICANT'S NAME (PLEASE PRINT)
Cook, Mark E. et al.

IF REISSUE, ORIGINAL PATENT NUMBER

ORIGINAL CLASSIFICATION

CLASS	SUBCLASS
424	442

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)			
424	283.1			
530	388.85	389.1	388.24	
426	92	89	140	
106	148.1	147.3	243	

INTERNATIONAL CLASSIFICATION

C	09	D		191/00
A	61	K		39/395
A	23	K		1/16
C	07	K		16/26

GROUP ART UNIT: 1816

ASSISTANT EXAMINER (PLEASE STAMP OR PRINT FULL NAME): F. Pierre VanderVegt

PRIMARY EXAMINER (PLEASE STAMP OR PRINT FULL NAME): David A. Saunders

PTO 270 (REV. 6-91)

ISSUE CLASSIFICATION SLIP

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

Claim Final	Claim Original	Date 2/10/97	Date 9/25/97	Date 11/10/97
	1	✓		=
	2			
	3			
	4			
	5			
	6		✓	
	7		✓	
	8	✓	✓	
	9		O	
	10		✓	
1	11		=	
	12			
	13			
	14			
	15			
	16			
	17			
	18			
	19			
	20			
	21			
	22			
	23			
	24			
	25			
	26			
	27			
	28			
	29			
	30			
	31			
	32			
	33			
	34			
	35			
	36			
	37			
	38			
	39			
	40			
	41			
	42		/	✓
	43			
	44			
	45			
	46			
	47			
	48			
	49			
	50			

SYMBOLS

✓	Rejected
=	Allowed
. (Through numeral)	Canceled
↓	Restricted
N	Non-elected
I	Interference
A	Appeal
O	Objected

Claim Final	Claim Original	Date
	51	
	52	
	53	
	54	
	55	
	56	
	57	
	58	
	59	
	60	
	61	
	62	
	63	
	64	
	65	
	66	
	67	
	68	
	69	
	70	
	71	
	72	
	73	
	74	
	75	
	76	
	77	
	78	
	79	
	80	
	81	
	82	
	83	
	84	
	85	
	86	
	87	
	88	
	89	
	90	
	91	
	92	
	93	
	94	
	95	
	96	
	97	
	98	
	99	
	100	

(LEFT INSIDE)

(FACE)

POSITION		ID NO.	DATE
CLASSIFIER		48	8/28/96
EXAMINER		Holloway	9-5-96
TYPIST		530	9-9-96
VERIFIER		277	9-13
CORPS CORR.			
SPEC. HAND			
FILE MAINT.			
DRAFTING			

INDEX OF CLAIMS

Claim Final	Claim Original	Date						
		2/10/99	9/25/99	11/10/99				
	1	✓	—					
	2							
	3							
	4							
	5							
	6							
	7		✓	✓				
	8		✓	✓				
	9		✓	✓				
	10		✓	O				
	11		✓	O				
1	12			=				
	13							
	14							
	15							
	16							
	17							
	18							
	19							
	20							
	21							
	22							
	23							
	24							
	25							
	26							
	27							
	28							
	29							
	30							
	31							
	32							
	33							
	34							
	35							
	36							
	37							
	38							
	39							
	40							
	41							
	42			✓				
	43							
	44							
	45							
	46							
	47							
	48							
	49							
	50							

SYMBOLS

✓ ..... Rejected
= ..... Allowed
- (Through numberal) Canceled
+ ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal
O ..... Objected

Claim Final	Claim Original	Date						
	51							
	52							
	53							
	54							
	55							
	56							
	57							
	58							
	59							
	60							
	61							
	62							
	63							
	64							
	65							
	66							
	67							
	68							
	69							
	70							
	71							
	72							
	73							
	74							
	75							
	76							
	77							
	78							
	79							
	80							
	81							
	82							
	83							
	84							
	85							
	86							
	87							
	88							
	89							
	90							
	91							
	92							
	93							
	94							
	95							
	96							
	97							
	98							
	99							
	100							

(LEFT INSIDE)

[redacted]

SEARCHED

Class	Sub.	Date	Exmr.
530	389.4, 389.5 390.1, 389.1 388.85	2/5/97	RV
424	442 157.1 159.1, 164.1 283.1		
106	197.3 148.1 243		
426	92, 89, 140		
UPDATED ABOVE		9/25/97	RV
530	389.1 388.85 388.24	11/10/97	RV
424	442 283.1		
426	92, 89, 140		
106	148.1 147.3 243		

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
530	389.1 388.85 388.24	11/10/97	RV
424	442 283.1		
426	92, 89 140		
106	148.1 147.3 243		

SEARCH NOTES

	Date	Exmr.
APS STN CLUSTER: AGRICULTURE	2/5/97	RV
08/576,703 AAU 08/576,597 AAU 08/576,508 AAU	2/6/97	RV
APS STN AGRICULTURE	9/25/97	RV
08/807,435 APS UPDATED STN UPDATED	11/10/97	RV

(RIGHT OUTSIDE)

PATENT APPLICATION SERIAL NO. 08/684785

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

330 UT 17-0055 08/01/96 08684785
33071 101 750.00CH

PTO-1556
(5/87)

BAR CODE LABEL

U.S. PATENT APPLICATION

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT
08/684,785	07/22/96	424	1816

APPLICANT

MARK E. COOK, MADISON, WI; DARIA L. JEROME, MIDDLETON, WI.

CONTINUING DATA********
VERIFIED

_____

FOREIGN/PCT APPLICATIONS********
VERIFIED

_____

FOREIGN FILING LICENSE GRANTED 09/09/96

STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS	FILING FEE RECEIVED	ATTORNEY DOCKET NO.
WI	0	8	2	$750.00	960296.94011

ADDRESS

THAD F KRYSHAK
QUARLES & BRADY
411 EAST WISCONSIN AVE
MILWAUKEE WI 53202-4497

TITLE

METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN

This is to certify that annexed hereto is a true copy from the records of the United States Patent and Trademark Office of the application which is identified above.

By authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

Date

Certifying Officer

08/684,785

ABSTRACT OF THE DISCLOSURE

A method of improving the efficiency of an animal to convert feed into desirable body tissue involves feeding the animal feed particles having an inner core of nutrients and an outer layer of fat containing antibodies which can protect the animal from contacting diseases that can adversely affect the animal's ability to grow or efficiently convert its feed into body tissue.

B/684785

METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN

Field Of The Invention

The present invention relates generally to the feeding of animals. More particularly, it relates to a method of improving the animal's growth or the efficiency of the animal to convert its feed into desirable body tissue (e.g. muscle) and compositions for use in the method.

Background Of The Invention

It is known that healthy, disease-free animals grow faster or are more able to convert their feed efficiently into body tissue than sick or immune-challenged animals. Obviously, faster growth or a more efficient conversion of feed into desirable body tissue in an animal is both economically and ecologically important, especially in animals raised for food. For this, and other reasons, it is desirable to prevent animals from contacting diseases.

One approach to keeping animals healthy is to give the animals antibiotics. However, that approach is not desirable for animals raised for food because there can be antibiotic residues in the food.

Another approach to keeping animals healthy is to immunize the animals. This can be done by vaccinating the animals against specific diseases to produce an active immunization or by administering to the animals antibodies to produce a passive immunization.

In U.S. Patent Nos. 4,748,018 and 5,080,895, methods are disclosed for passively immunizing animals against intestinal diseases which could interfere with the animal's efficient conversion of feed. The patented methods basically comprise orally administering to said animals

effective amounts of egg-derived materials containing avian antibodies which are obtained by immunizing egg-laying hens with specific antigens which will produce such antibodies, and obtaining the antibody containing material from eggs laid by the hen. In both patents, the antibody containing egg materials are reduced to powders and fed to the animals to be passively immunized.

Brief Summary Of The Invention

It is the primary object of the present invention to disclose a novel method to improve the animals growth or the efficiency of the animal to convert its feed into desirable body tissue.

Another object of the invention is to disclose an animal feed for animals for use in the inventive method.

The method of the present invention to improve the animals growth or the efficiency of the animal to convert its feed into desirable body tissue comprises orally administering to said animal feed particles having an inner core comprising primarily non-fat nutrients and an outer layer of fat which contains a safe and effective amount of antibodies that help protect the animal from disease or other antigens that can adversely affect the animal's growth or the efficiency of the animal to convert feed into desirable body tissue.

The compositions of the present invention are animal feed particles having an inner core comprised of nutrients, such as proteins and carbohydrates, and an outer layer of fat that contains the antibodies encapsulated therein.

The compositions of the present invention are conveniently made by first forming a nutrient mixture to produce an inner core, and then coating the outer surface of the core with a layer of fat containing antibodies

encapsulated therein so the antibody is stabilized and substantially protected against antibody destroying factors, such as environmental conditions and intestinal proteases.

In an especially preferred embodiment of the invention, the antibodies in the fat are obtained from the egg of a hen which has been injected with an antigen that results in the production by the hen of those antibodies.

The compositions of the present invention are superior to previously known animal feeds in which antibody-containing powders were mixed with nutrients, including fat, and then granulated or extruded because the fat layer in the method of the present invention is applied to the core after the pelletization, extrusion, granulation or expansion process. As a result the antibodies in the outer fat layer of the compositions of the present invention are not degraded by the elevated temperatures that can arise during the pelletization, granulation, extrusion or expansion process. The compositions of the present invention are also superior to prior art feeds because the outer layer of fat in which the antibodies are encapsulated helps protect the antibodies from stomach acid and intestinal enzymes.

Description Of The Preferred Embodiment

In the preferred embodiment of the present invention, the animal feed particles comprise an extruded inner core which contains primarily the desired non-fat materials, such as proteins and carbohydrates, and an outer layer of fat which contains the antibodies encapsulated therein. The outer layer also can contain other ingredients, such as oil soluble vitamins and the inner core can, of course, also contain fat, if desired.

In the preferred practice of the method of invention, the animal feed with the antibody-containing outer layer is

orally fed to the animal in an amount which will passively immunize the animal.

The antibodies for use in the present invention are those which can alter physiological processes that adversely affect growth and feed efficiency. They can be antibodies that are against diseases or specific endogenous regulators of food intake and gastrointestinal motility. The antibodies are preferably derived from the eggs of hens which have been previously immunized to produce those antibodies as described in U.S. Patent No. 4,748,018 or U.S. Patent No. 5,080,895. Especially preferred as the antibody-containing material are spray dried egg yolks and whole eggs. However, other non-egg derived antibody-containing materials may be used.

The preferred inner core for the animal feed particles is an extrusion which contains a mixture of nutrients, such as grains, with or without added sugars, carbohydrates and/or proteins. The core will normally contain less than the desired total amount of the dietary fat for the animal because of the fat in the outer layer.

The fat for use in the outer layer to encapsulate and protect the antibody can be any fat or lipid, which can be readily mixed with the antibody containing material to form a mixture, which contains the antibody encapsulated therein and which can be readily sprayed or otherwise coated on the outer surface of the core. Especially preferred are those fats which are solid at ambient temperatures and which will protect the antibodies from adverse environmental conditions and intestinal enzymes. Especially preferred as the fat is a mixture of tallow and conjugated linoleic acid (CLA) which also is known to increase feed efficiency.

Representative of other fats that can be used are the following:

Lard
Yellow Grease
Poultry Fat
Spent Restaurant Oil
Animal Oils
Vegetable Oils
Fish Oils
Oil Derivatives, i.e., lecithin
and
Mixtures thereof.

The practice of the present invention is further illustrated by the following examples:

Example 1

Preparation Of Antibodies.

An antigen, such as cholecystokinin peptide which produces cholecystokinin (CCK) antibodies, is injected intramuscularly into mature hens at a dose of about 50 mg to 1000 mg with a water-in-oil emulsion adjuvant. Samples of the whole eggs or yolks of eggs from the hens are assayed by known methods for CCK antibody content. When the CCK antibody titer reaches a maximum level, the whole eggs or yolks of eggs are collected and pooled, homogenized and spray dried to obtain a powder.

Example 2

Preparation Of Animal Feed Particles With Outer Layer Of Fat Containing Antibodies.

A CCK antibody-containing powder made by the process of Example 1 is mixed with tallow to form a blend in which the powder is substantially encapsulated by the fat. The fat mixture is then spray coated upon inner cores made by the pelletization, the granulation, the extrusion or the expansion of a plasticized mixture of nutrients, including carbohydrate, protein and water. The resulting animal feed

particles have an inner core of nutrients and an outer layer of fat containing CCK antibodies.

Example 3

Animal Feeding Test.

Ducks are fed the animal feed of Example 2 and their biological responses are determined. It is found that the ducks receiving the animal feed of Example 2 demonstrate an improved body weight gain and a more efficient rate of feed conversion than control ducks.

Table 1 shows the results obtained in 14 day old ducks fed a control feed and an otherwise identical feed (BRAVO) having an outer antibody-containing layer.

TABLE 1

	ABOVE BODY WEIGHT SUMMARY			(Lbs)	
TREATMENT		14 day weight	27 day weight	14-27 day gain	
Control		1.45	4.48	3.02	
Bravo		1.39	4.32	2.93	
TREATMENT		39 day weight	14-39 day gain		
Control		6.93	5.48		
Bravo		7.11	5.72		
		FEED CONVERSION DATA			
Treatment		14-27 feed/bird	0-27 feed/bw*	14-17 feed/gain	
Control		5.50	1.229	1.819	
Bravo		5.16	1.192	1.758	
Treatment		14-39 feed/bird	0-39 feed/bw*	14-39 feed/gain	
Control		11.783	1.720	2.170	
Bravo		10.859	1.530	1.904	

* bw = body weight

It will be apparent to those skilled in the art that the present invention can be used to prepare the animal feed for a wide variety of food animals, including without limitation, ducks, chickens and turkeys.

It also will be readily apparent to those skilled in the art that a large number of changes and modifications can be made without departing from the spirit and scope of the present invention. Therefore, it is intended that the invention only be limited by the claims which follow.

We claim:

1. A method to improve the growth of an animal or the efficiency of an animal to convert feed into desired body tissue, said method comprising feeding an animal an effective amount of animal feed particles comprising an inner core of nutrients and an outer layer of fat having antibodies encapsulated therein,

said antibodies being antibodies that can passively immunize the animal against the adverse effects of an antigen which could reduce the animal's ability to grow or to efficiently convert its feed into desirable body tissue.

2. A method of Claim 1 in which the antibodies are derived from a chicken egg.

3. A method of Claim 1 in which the fat is an edible fat.

4. A method of Claim 1 in which the fat is one which protects the antibodies from adverse environmental conditions.

5. A method of Claim 1 in which the fat is a mixture of a conjugated linoleic acid and another fat.

6. A particulate animal feed comprising an inner core of nutrients containing carbohydrates and proteins and an outer layer of an edible fat having antibodies encapsulated therein.

7. An animal feed of Claim 6 in which the antibodies are derived from a chicken egg.

8. An animal feed of Claim 6 in which the fat is a mixture of a conjugated linoleic acid and another fat.

add
claim

ADD
B1 claim

DECLARATION AND POWER OF ATTORNEY FOR DESIGN AND UTILITY PATENT APPLICATION	ATTORNEY'S DOCKET NO.: 960296.94011

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN the specification of which (check one) [X] is attached hereto, [ ] was filed on _____ as Application No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed: None

(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed [] Yes [] No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

(Application No.)	(Filing Date)

I hereby claim benefit under Title 35, United States Code §120 of any United States application(s) listed below, and insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided in the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

(Application No.)	(Filing Date)	(Status - patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and all continuation and divisional applications based thereon, and to transact all business in the Patent and Trademark Office connected therewith: Thad F. Kryshak, Reg. No. 19,428; Carl R. Schwartz, Reg. No. 29,437; Jean C. Baker. Direct all telephone calls to Thad F. Kryshak at telephone no. (414) 277-5781. Address all correspondence to: Thad F. Kryshak c/o Quarles & Brady, 411 East Wisconsin Ave., Milwaukee, WI 53202-4497.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF SOLE OR FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
Mark E. Cook	Mark E. Cook	7/19/96
RESIDENCE		**CITIZENSHIP**
Madison, WI Wisconsin 53705		U.S.A.
POST OFFICE ADDRESS		
15 Kewaunee Court, Madison, WI 53705		

FULL NAME OF SECOND JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Daria L. Jerome	Daria L. Jerome	7-19-96
RESIDENCE		**CITIZENSHIP**
Middleton, WI Wisconsin 53562		U.S.A.
POST OFFICE ADDRESS		
5730 Highland Way, Apt. 204, Middleton, WI 53562		

411 East Wisconsin Avenue
Milwaukee, Wisconsin 53202-4497
414/277-5000
FAX 414/271-3552

Attorneys at Law in
Milwaukee and Madison, Wisconsin
West Palm Beach and Naples, Florida
Phoenix, Arizona

08/684785

Quarles & Brady

PATENT

Box Patent Application
Assistant Commissioner For Patents
Washington, D.C. 20231

July 22, 1996

Sir:

Our Case No. 960296.94011

Transmitted herewith for filing is the patent application of Inventor(s): Mark E. Cook
Daria L. Jerome

For: METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN

Enclosed are also:

[ ] __ sheet(s) of drawing.

[ ] Information Disclosure Statement

CLAIMS AS FILED

For	Number Filed	Number Extra	Rate	Basic Fee $750.00
Total Claims	8 - 20 =	0 X	$ 22.00	= 0
Independent Claims	2 - 3 =	0 X	$ 78.00	= 0
Multiple Dependent Claim.....			$250.00	= 0
Total Filing Fee				$750.00

[X] Please charge our Deposit Account No. 17-0055 in the amount of $750.00. Two extra copies of this sheet are enclosed.

[X] The Commissioner is hereby authorized to charge any additional filing fees which may be required under 37 CFR 1.16, or credit any overpayment to Account No. 17-0055. Two extra copies of this sheet are enclosed.

[ ] A check for $ .00 to cover the filing fee and the cost of recording the assignment is enclosed.

Respectfully submitted,

Thad F. Kryshak, Esq.
Reg. No. 19,428

QB1\323680.1

Express Mail" mailing label
number EG640607585 US
Date of Deposit 7-22-96

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231

MAIL ROOM JUL 22 1996

Thad F. Kryshak Reg. No. 19,428
(Name of person making deposit)

#2
11/9/98

PATENT

I hereby certify that this correspondence is being deposited with the United States Postal Services on the date set forth below as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington DC 20231.
Date of Signature and Deposit: 10/2/96

Attorney of Record

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Mark E. Cook et al.
Serial No.:	08/684,785
Filed:	JULY 22, 1996
For:	METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN
Group Art Unit:	1816
Examiner:	---

DISCLOSURE STATEMENT UNDER 37 C.F.R 1.97 AND 1.98

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The following references are submitted to the Patent and Trademark Office for consideration in the above-identified application in satisfaction of Applicant's duty of disclosure as provided for in 35 C.F.R. 1.97 and 1.98. No full patent search was conducted and the Applicants make no representation that better art than the following is not available.

1. Polson, U.S. Patent No. 4,357,272. This patent discloses methods of recovering purified antibodies from egg yolk.

2. Polson, U.S. Patent No. 4,550,019. This patent discloses the manufacture and use of fowl egg antibodies.

3. Stolle et al., U.S. Patent No. 4,748,018. This patent discloses a method of passive immunization of mammals using avian antibodies.

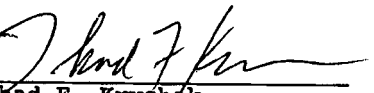
4. Tokoro, U.S. Patent No. 5,080,895. This patent discloses an antibody containing substances from eggs, a method of producing it and its use.

5. Cook et al., U.S. Patent No. 5,428,072. This patent discloses a method of increasing the efficiency of feed conversion in animals using a conjugated linoleic acid.

None of the above references are believed to disclose or suggest the present invention.

Respectfully submitted,

MARK E. COOK
DARIA L. JEROME

By: 

Thad F. Kryshak
Reg. No. 19,428
Quarles & Brady
411 East Wisconsin Avenue
Milwaukee, WI 532-24497
414-277-5781

Form PTO-1449
(Rev. 2-88)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ATTY. DOCKET: 960296.94011

APPLICATION NO. 08/684,785

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

APPLICANT: Mark E. Cook et al.

FILING DATE: 07/22/96

GROUP: 1816

(Use several sheets if necessary)

U.S. PATENT DOCUMENTS

EXAMINER'S INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
B/	A1	4,357,272	11/02/82	Polson	~~260~~	~~112~~	03/15/79
	B1	4,550,019	10/29/85	Polson	~~424~~	~~85~~	07/16/82
	C1	4,748,018	05/31/88	Stolle et al.	~~424~~	~~87~~	06/19/84
	D1	5,080,895	01/14/92	Tokoro	~~424~~	~~85~~	04/01/91
	E1	5,428,072	06/27/95	Cook et al.	514	560	01/22/93

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*

EXAMINER: [signature] DATE CONSIDERED: 2/5/97

* EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

QB1\295505.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/684,785	07/22/96	COOK, M	960296.94011

THAD F KRYSHAK
QUARLES & BRADY
411 EAST WISCONSIN AVE
MILWAUKEE WI 53202-4497

18M1/0218

EXAMINER	
VANDERVEGT,F	

ART UNIT	PAPER NUMBER
1816	

DATE MAILED: 02/18/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (REV. 2/95)

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

1-File Copy

Office Action Summary

Application No.	Applicant(s)
08/684,785	Cook et al
Examiner	**Group Art Unit**
F. Pierre VanderVegt	1816

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-8* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-8 are pending in this application.

Claim Rejections - 35 USC § 112

1. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for providing animals with antibody to cholecystokinin (CCK), does not reasonably provide enablement for passively immunizing an animal against antigens which could reduce the animal's ability to grow or to efficiently convert its feed into desirable body tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses immunization of hens with CCK and feeding the antibodies to CCK obtained from their eggs to ducks. CCK is a natural peptide secreted by the mucosa of the upper intestine which stimulates contraction of the gall bladder and secretion of pancreatic enzymes which are desirable events in the digestion process. The specification does not provide guidance how to determine antigens which could reduce the animal's ability to grow or to efficiently convert its feed into desirable body tissue. Given the nature of the invention, which is to enhance the digestive process, it would require undue experimentation on the part of a skilled artisan to determine which other antigens that are active in digestive processes would be suitable as targets for antibodies which are administered orally by the method of the present invention. Further, the specification provides no guidance as to which antigens to which the animal is exposed from external sources would be suitable immunogens for use in the present invention.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the nature of the invention, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(C) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook et al, U.S. Patent 5,428,072 (E1 on form PTO-1449), in view of Tokoro et al, U. S. Patent 5,080,895 (D1), Albright et al (U on form PTO-892) and Ludington et al, U.S. Patent 3,119,691 (A).

The '072 patent teaches a method and composition to improve the efficiency of feed conversion in an animal comprising adding to the feed of the animal an effective amount of conjugated linoleic acid (CLA; Abstract and column 1, lines 54-68 in particular). The '072 patent further shows that chicks fed the CLA as a supplement required less standard poultry feed for equivalent weight gain to controls receiving unsupplemented standard poultry feed (Example 1 in particular). The '072 patent also teaches that the CLA had to be mixed with the feed on a daily basis (Examples 2 & 3 in particular). The '072 patent does not teach antibodies encapsulated in fat as a coating for feed particles. The '895 patent teaches a method for immunizing female chickens with an antigen, such as a pathogenic bacteria, and obtaining

an antibody preparation to said antigen from the eggs of the chickens which is processed into a dry powder (Example 1 in particular. The '895 patent further teaches that this preparation is useful for protecting animals from the pathogen used to immunize the chicken and exemplifies this by feeding the preparation to neonatal pigs (Example III in particular). The combination of references does not teach encapsulation of the antibody or CLA in protective fat as a coating for food particles. Albright et al teaches the encapsulation of vitamin a, another dietary supplement, in a lipid composition which protects the Vitamin a from mineral catalyzed degradation and hydrolysis for extended periods of time (see entire document). The combination of references does not teach coating of feed particles. The '691 patent teaches coating animal food particles by spraying with fat which melts when warmed but solidifies at room temperature (column 4, line 66 through column 5, line 22 in particular). The '691 patent also teaches that said fat may have a powder dispersed in it (column 5, lines 31-37 in particular). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the anti-pathogen antibodies of the '895 patent and the feed conversion enhancing CLA of the '072 patent with the protective fat coating taught by Albright et al and spray the mixture as a coating on an animal feed product. One would have been motivated to combine these teachings with a reasonable expectation of success by the desire to protect animals, such as a commercial livestock, from specific pathogens using easily produced and prepared antibodies to the pathogen and protect the antibody molecules from degradative forces during storage using fat encapsulation. One would have been further motivated to add the CLA in order to reduce the amount of feed required by the animals to thrive and to apply the mixture directly to the food particles as a a coating in order to control the amount of supplement delivered to the animals relative to the amount of food given, without having to mix each time the animals are fed and non-intake of the supplements due to settling of powders out of pelletized foods. Motivation to provide these supplements as a coating, rather than admixed directly with the nutrients of the food pellet, is provided by the

fact that some animal feed products must be heated during processing to temperatures which would destroy the antibodies.

Conclusion

4. Papers related to this application may be submitted to group 1800 by facsimile transmission. Papers should be faxed to group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for Art Unit 1816 is (703)308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The examiner can normally be reached Monday through Friday from 8:00 am to 4:30 pm ET. a message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the group 1800 receptionist, whose telephone number is (703)308-0196.

February 11, 1997
F. Pierre VanderVegt, Ph.D.
Patent Examiner
Art Unit 1816

Christina Chan

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP 1800

Notice of References Cited

Application No.	Applicant(s)		
08/684,785	Cook et al		
Examiner		Group Art Unit	Page 1 of 1
F. Pierre VanderVegt		1816	

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
A	3,119,691	1-28-64	Ludington et al	99	2
B					
C					
D					
E					
F					
G					
H					
I					
J					
K					
L					
M					

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
N						
O						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
U	Albright, RB et al. Drug. Dev. Ind. Pharm. 20(12):2035-2039.	7/94
V		
W		
X		

PATENT 1816

I hereby certify that this correspondence is being deposited with the United States Postal Service on the date set forth below as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231
and Deposit June 5, 1997

Thad F. Kryshak, Reg. No. 19,428

#4 7/22/97

MAIL ROOM JUN 9 1997 PAT. & TRADEMARK OFF.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Mark E. Cook et al.
Serial No.: 08/684,785
Filed: July 22, 1996
For: METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN
Group Art Unit: 1816
Examiner: F. Pierre VanderVegt

RECEIVED
JUL 18 1997
GROUP 1800

PETITION AND FEE FOR EXTENSION OF TIME
(37 CFR 1.136(a))

Assistant Commissioner For Patents
Washington, D.C. 20231

Sir:

Applicant hereby petitions the Commissioner of Patents and Trademarks to extend the time for response to the Office Action dated February 18, 1997 for one month from May 18, 1997 to June 18, 1997.

Applicant is
- [ ] a small entity, A verified statement for which:
  - [ ] is attached.
  - [ ] was filed previously.
- [X] other than a small entity.

Extension:

Months	Fee for Non-Small Entity	Fee for Small Entity	
[X] one month	$110.00	$55.00	
[ ] two months	$390.00	$195.00	
[ ] three months	$930.00	$465.00	
[ ] four months	$1470.00	$735.00	Fee $110.00

Please charge the above-identified fee to Deposit Account No. 17-0055. Any additional fee due in this application and any overpayment should be charged or credited to Deposit Account No. 17-0055. A duplicate copy of this paper is enclosed.

A response to the Office Action
- [X] is filed herewith.
- [ ] has been filed.

Respectfully submitted,

Dated:

By: Thad F. Kryshak, Esq.
Registration No. 19,428

Quarles and Brady
411 East Wisconsin Ave.
Milwaukee, WI 53202
(414) 277-5781

07/16/1997 08684785 17-0055 01 FC:115

MKE\4004489.01

#5/A
C
7/22/97

PATENT

I hereby certify that this correspondence is being deposited with the United States Postal Services on the date set forth below as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington DC 20231.

Date of Signature and Deposit: June 5, 1997

Attorney of Record

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Mark E. Cook et al.
Serial No.:	08/684,785
Filed:	July 22, 1996
For:	METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN
Group Art Unit:	1816
Examiner:	F. Pierre VanderVegt

AMENDMENT

Assistant Commissioner for Patents
Washington DC 20231

Dear Sir:

In response to the Office Action of February 18, 1997, please amend the claims as follows:

IN THE CLAIMS:

Cancel claims 1 to 5.

Add the following new claims:

9. An animal feed of claim 6 in which the antibodies are cholecystokinin (CCK) antibodies.

QB1\380757.1

a1 10. A method of administering antibodies to an animal, said method comprising feeding to said animals an animal feed of claim 6

REMARKS

A reconsideration of this application is respectfully requested. In the Office Action, claims 1 to 5 were rejected under 35 U.S.C. § 112 on the grounds that the specification was not enabling. In the present amendment, claims 1 to 5 have been canceled. The rejection which was applied to original claims 1 to 5 is not believed to be applicable to new claims 9 and 10, which depend from claim 6, and more clearly define the applicant's invention.

Prior to discussing the rejection of the original claims based on the cited art, the Applicant would like to point out that the invention of the present claims is a novel animal feed which solves a long-standing need for a simple and efficient way of administering all types of antibodies to animals without the antibodies being inactivated in the processing of the feed into pellets or in the intestinal tract of the animal or by the environment. Accompanying this amendment is the Declaration of Dr. Cook, who is one of the inventors of the present application and an inventor of the Cook et. al., U.S. Patent No. 5,428,072, which was the primary reference relied upon by the Examiner in rejecting the

claims. Dr. Cook's declaration supports the conclusion that the invention of the present application was not obvious to those skilled in the art at the time the invention was made.

In the Office Action, the Examiner relies combines four unrelated references to reject the Applicant's claims as unpatentable. Of these four references, the Examiner relies upon the Cook et. al. '072 patent as the primary reference, but admits that "The '072 Patent does not teach antibodies encapsulated in fat as a coating for feed particles". The Examiner also states that the Tokoro et. al., '895 patent, which relates to the immunization of chickens with an antigen to obtain antibodies that can be used in the practice of the Applicant's invention fails to teach encapsulation of the antibody or CLA in protective fat as a coating for food particles. The Examiner further admits that the Albright et. al. reference that teaches the encapsulation of Vitamin E does not teach a coating of feed articles. Nevertheless, the Examiner combines the above three references with the Ludington et. al. '691 patent, which teaches the coating of dog food particles by spraying them with a gravy mix which contains fat, and concludes that it would be obvious to one skilled in the art to combine the teachings of those four references to come up with the Applicant's invention. However, since there is no suggestion in any of the prior art that this combination of references should or could be made, it is

evident that in this case the conclusion of obviousness is reached by using hindsight. Furthermore, it is important to note that combining the references as suggested by the Examiner would not result in the Applicant's novel animal feed. Instead, it would result in a product like that of Ludington, et al. that has an outer layer that dissolves in water. Such an outer layer would not protect the antibodies, but help to destroy them. Thus, the combination of the references would result in a product that does not accomplish the same goal as Applicant's animal feed.

As can be seen from the accompanying declaration of Dr. Cook, it would not have been obvious from the prior art that an outer layer of fat containing antibodies applied to particles of animal feed after pelleting would result in a useful product for a number of reasons, including the "insurmountable obstacles" reported by others in connection with the application of an analogous method to vitamins (See Exhibit A, which accompanies the Cook Declaration, especially page 104). One skilled in the art would believe that the same sort of "insurmountable obstacles" would exist if one were to try to protect antibodies. Thus, the prior art actually leads one skilled in the art away from the Applicant's invention.

Furthermore, as pointed out in Dr. Cook's declaration, there was no way of his knowing in advance whether the Applicant's coated particles would have the

same desired activity as was obtained when the antibodies were uniformly blended into mash feed.

Dr. Cook points out in his declaration, a number of other reasons why one skilled in the art would assume that the Applicant's approach may not have worked. For example, the antibodies in the fat in the outer layer on the extruded or pelleted cores might be exposed to air rendering them more subject to oxidation than if they were in the core itself. In addition, the antibodies might be more readily destroyed because the outer layer which contains the antibodies is the first part of the animal feed to be exposed to gastric HCL, which has a pH as low as 2 and digestive processes in the animal, and thus the antibodies might be less buffered than if they were in the core.

In addition as Dr. Cook notes, the post manufacturing handling of pelleted and extruded feeds can result in the productions of fines, which are not consumed by animals unless they are forced to do so. Furthermore, since fines originate from the surface material of the particles, such fines could be rich in antibodies, and it would be reasonable to assume that the coating of the particles with an outer layer that contains antibodies actually could actually result in lower levels of antibody being consumed by the animals.

There is nothing in the cited prior art that would in any way suggest the novel animal feed of the present invention which solves the problem of how to obtain both

the advantages of pelleting feed and administering antibodies to animals.

In view of the foregoing, it is respectfully submitted that the Applicant's novel animal feed particles which are coated with an outer layer of antibodies in fat are not only novel, but also unobvious. Therefore it is believed that the claims, as amended, are allowable and that a Notice of Allowance should be forthcoming.

Respectfully submitted,

MARK E. COOK
DARIA L. JEROME

By: 

Thad F. Kryshak
Reg. No. 19,428
Quarles & Brady
411 East Wisconsin Avenue
Milwaukee, WI 532-24497
414-277-5781

PTO/SB/17 (6-95)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

U.S. Department of Commerce
Patent and Trademark Office

FEE TRANSMITTAL

TOTAL AMOUNT OF PAYMENT	$110.00

Complete If Known	
Application Number	08/684,785
Filing Date	July 22, 1996
First Named Inventor	Mark E. Cook
Group Art Unit	1816
Examiner Name	F. Pierre VanderVegt
Attorney Docket Number	960296

RECEIVED
JUN 13 1997
GROUP 1800

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 17-0055

Deposit Account Name: Quarles & Brady

[X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17 [ ] Charge the Issue Fee Set in 37 CFR 1.18 at the Mailing of the Notice of Allowance, 37 CFR 1.311(b)

2. [ ] Payment Enclosed: [ ] Check [ ] Money Order [ ] Other

FEE CALCULATION (fees effective 10/01/96)

1. FILING FEE

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
101	770	201	385	Utility filing fee	
106	320	206	160	Design filing fee	
107	530	207	265	Plant filing fee	
108	770	208	385	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($)0

2. CLAIMS

		Extra		Fee from below		Fee Paid
Total Claims	2	-20 =	0	X	=	
Independent Claims	2	-3 =	0	X	=	
Multiple Dependent Claims					=	

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	260	204	130	Multiple dependent claim
109	80	209	40	Reissue independent claims over original patent
110	22	210	11	Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)0

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,460	147	2,460	For filing a request for reexamination	
112	*900	112	*900	Requesting publication of SIR prior to Examiner action	
113	*1,790	113	*1,790	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for response within first month	$110
116	390	216	195	Extension for response within second month	
117	930	217	465	Extension for response within third month	
118	1,470	218	735	Extension for response within fourth month	
119	300	219	150	Notice of Appeal	
120	300	220	150	Filing a brief in support of an appeal	
121	260	221	130	Request for oral hearing	
138	1,470	138	1,470	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive unavoidably abandoned application	
141	1,280	241	645	Petition to revive unintentionally abandoned application	
142	1,290	242	645	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	650	244	325	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	230	126	230	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	770	246	385	Filing a submission after final rejection (37 CFR 1.129(a))	
149	770	249	385	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____ $

Other fee (specify) _____

SUBTOTAL (3) ($)110

* Reduced by Basic Filing Fee Paid

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	Thad F. Kryshak, Esq.			Reg. Number	19,428
Signature	Thad F Kryshak	Date	June 5, 1997	Deposit Account User ID	

PTO/SB/17 (6-95)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

002/PTO
Rev. 10/96

U.S. Department of Commerce
Patent and Trademark Office

FEE TRANSMITTAL

TOTAL AMOUNT OF PAYMENT	$110.00

Complete if Known	
Application Number	08/684,785
Filing Date	July 22, 1996
First Named Inventor	Mark E. Cook
Group Art Unit	1816
Examiner Name	F. Pierre VanderVegt
Attorney Docket Number	960296.94011

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 17-0055

Deposit Account Name: Quarles & Brady

[X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17 [ ] Charge the Issue Fee Set in 37 CFR 1.18 at the Mailing of the Notice of Allowance, 37 CFR 1.311(b)

2. [ ] Payment Enclosed: [ ] Check [ ] Money Order [ ] Other

FEE CALCULATION (fees effective 10/01/96)

1. FILING FEE

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
101	770	201	385	Utility filing fee	
106	320	206	160	Design filing fee	
107	530	207	265	Plant filing fee	
108	770	208	385	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($)0

2. CLAIMS

			Extra		Fee from below		Fee Paid
Total Claims	2	-20=	0	X		=	
Independent Claims	2	-3=	0	X		=	
Multiple Dependent Claims						=	

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	260	204	130	Multiple dependent claim
109	80	209	40	Reissue independent claims over original patent
110	22	210	11	Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)0

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,460	147	2,460	For filing a request for reexamination	
112	*900	112	*900	Requesting publication of SIR prior to Examiner action	
113	*1,790	113	*1,790	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for response within first month	$110
116	390	216	195	Extension for response within second month	
117	930	217	465	Extension for response within third month	
118	1,470	218	735	Extension for response within fourth month	
119	300	219	150	Notice of Appeal	
120	300	220	150	Filing a brief in support of an appeal	
121	260	221	130	Request for oral hearing	
138	1,470	138	1,470	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive unavoidably abandoned application	
141	1,280	241	645	Petition to revive unintentionally abandoned application	
142	1,290	242	645	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	650	244	325	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	230	126	230	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	770	246	385	Filing a submission after final rejection (37 CFR 1.129(a))	
149	770	249	385	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____ $

Other fee (specify) _____

SUBTOTAL (3) ($)110

* Reduced by Basic Filing Fee Paid

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	Thad F. Kryshak, Esq.			Reg. Number	19,428
Signature	Thad F Kryshak	Date	June 5, 1997	Deposit Account User ID	

PTO/SB/17 (6-95)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

002/PTO
Rev. 10/96

U.S. Department of Commerce
Patent and Trademark Office

FEE TRANSMITTAL

TOTAL AMOUNT OF PAYMENT	$110.00

Complete If Known	
Application Number	08/684,785
Filing Date	July 22, 1996
First Named Inventor	Mark E. Cook
Group Art Unit	1816
Examiner Name	F. Pierre VanderVegt
Attorney Docket Number	960296.94011

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 17-0055

Deposit Account Name: Quarles & Brady

[X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17 [ ] Charge the Issue Fee Set in 37 CFR 1.18 at the Mailing of the Notice of Allowance, 37 CFR 1.311(b)

2. [ ] Payment Enclosed: [ ] Check [ ] Money Order [ ] Other

FEE CALCULATION (fees effective 10/01/96)

1. FILING FEE

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
101	770	201	385	Utility filing fee	
106	320	206	160	Design filing fee	
107	530	207	265	Plant filing fee	
108	770	208	385	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($)0

2. CLAIMS

			Extra		Fee from below		Fee Paid
Total Claims	2	-20=	0	X		=	
Independent Claims	2	-3=	0	X		=	
Multiple Dependent Claims						=	

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	260	204	130	Multiple dependent claim
109	80	209	40	Reissue independent claims over original patent
110	22	210	11	Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)0

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,460	147	2,460	For filing a request for reexamination	
112	*900	112	*900	Requesting publication of SIR prior to Examiner action	
113	*1,790	113	*1,790	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for response within first month	$110
116	390	216	195	Extension for response within second month	
117	930	217	465	Extension for response within third month	
118	1,470	218	735	Extension for response within fourth month	
119	300	219	150	Notice of Appeal	
120	300	220	150	Filing a brief in support of an appeal	
121	260	221	130	Request for oral hearing	
138	1,470	138	1,470	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive unavoidably abandoned application	
141	1,280	241	645	Petition to revive unintentionally abandoned application	
142	1,290	242	645	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	650	244	325	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	230	126	230	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	770	246	385	Filing a submission after final rejection (37 CFR 1.129(a))	
149	770	249	385	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____ $

Other fee (specify) _____

SUBTOTAL (3) ($)110

* Reduced by Basic Filing Fee Paid

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	Thad F. Kryshak, Esq.			Reg. Number	19,428
Signature	Thad F. Kryshak	Date	June 5, 1997	Deposit Account User ID	

Burden Hour Statement: This form is estimated to take .2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. (Q81/4009098)

#6
(Coff.
7/22/97

I hereby certify that this correspondence is being deposited with the United States Postal Service on the date set forth below as First Class in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.
Date of Signature
and Deposit: June 5, 1997

Attorney of Record

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Mark E. Cook et al.	Group Art Unit: 1816
Serial No.:	08/684,785	
Filed:	July 22, 1996	
For:	METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN	
Examiner:	F. Pierre Vandervegt	

DECLARATION OF MARK E. COOK

I, Mark E. Cook, declare and state that:

1. A copy of my Curriculum Vitae is attached hereto.

2. I have reviewed the Official Action and the cited prior art in the above application, and I do not agree with the Examiner that the original claims are obvious and unpatentable over the Cook et al., U.S. Patent No. 5,428,072 in view of Tokoro et al., U.S. Patent No. 5,080,895, Albright et al. and Ludington et al., U.S. Patent No. 3,119,691.

3. There is nothing in any of the cited references, taken alone or in combination, which would make it obvious to me or an ordinary person skilled in the art that putting antibodies in fat and using the mixture to coat the outside of particles of animal feed would preserve antibody activity and be better than simply adding the antibodies to a feed mash.

4. It is well known that antibodies can be made to most any antigen using laying hens (see U.S. Patent No. 5,080,895, which we cited to the Patent Office). In the present application, we disclose that antibodies can be made to small peptides, such as CCK, and that these antibodies, when added to feed, can improve animal performance. We know that antibodies can be made to any antigens that are found in the lumen of the gastrointestinal tract of an animal. We also know that if the antigens have potential harmful effects (e.g. CCK) under given conditions, then feeding the antibodies for that antigen to an animal will normally prevent or counteract those effects. For example, whenever an animal is immune-stimulated, it goes off of its feed partly because of the cytokines (e.g. IL-1) that are released by the immune-stimulated cells (macrophages), which in turn cause a release of CCK which induces anorexia, thus decreasing performance. The cited Tokoro U.S. Patent No. 5,080,895, describes antibodies that like CCK show beneficial effects when added to animal's feed.

5. While the beneficial effects of adding antibodies to an animal's feed are known to those skilled in the art, there exists a real and previously unsolved application problem. Many feed producers produce pellets because they are preferred by animal growers to a feed mash. However, antibody IgG is denatured at a temperature of 70°C and there is a trend of pelleting feed at higher temperatures (from 71°C to 98°C). Furthermore, a rapidly growing method of feed processing is by extrusion, where temperatures can be

as high as 121°C to 149°C. Unfortunately antibodies, such as the egg yolk antibodies, do not survive the high temperatures of the pelleting or extrusion processes.

6. It would not have been obvious to one of ordinary skill in the art that a solution to the antibody denaturation problem could be achieved by applying an outer layer of fat and antibodies to particles of feed pellets because "insurmountable obstacles" had been reported previously in connection with the analogous application of vitamins to feed particles (see appendix A, page 104). It also was not known whether such a coated particle of animal feed would have the same bioactivity as observed when the antibodies were uniformly blended into feed. Before our invention, the only reported way egg yolk antibodies could be efficiently added to an animal's feed was to simply mix it with the feed mash.

7. The Cook et al., U.S. Patent No. 5,428,072, discloses a method of improving feed conversion by feeding the animal CLA. However, as admitted by the Examiner, that patent does <u>not</u> disclose coating the outside of a feed particle with an outer layer of fat and antibodies or using CLA as a blend with egg yolk antibodies.

8. The Tokoro patent teaches only how to produce antibodies, it does not suggest or teach how to protect them and preserve them in animal feed.

9. The Albright paper describes the encapsulation of vitamin A, which in turn is added to a vitamin/mineral

premix. However, there is no suggestion or teaching of an animal feed having an outer layer of fat and antibodies.

10. The Ludington et al., U.S. Patent No. 3,110,691, describes the coating of extruded pet foods with an outer layer which contains fat to prevent the extruded product from hydration when water is added to said product. The whole purpose of the invention of this patent is to prevent the formation of gummy, sticky particles, which might interfere with the formation of a gravy when water is added to the dog food. There is no mention of adding antibodies for any purpose. The outer layer of Ludington wouldn't work for antibodies because it would be solubilized off of a core particle of animal feed as soon as water is added (e.g. in G.I. tract). This would result in the exposure of biologically active antibodies to the destructive conditions of the upper GI tract long before they reach their biologically active site in the mid-GI tract.

11. None of the prior art leads one skilled in the art to the conclusion that particles of animal feed should be coated with an outer layer of egg yolk antibodies in fat, and that the antibodies in the outer layer would retain their biological activity. In fact, the prior art discloses several reasons why one skilled in the art would not have believed that this approach would work. They are: (1) the antibodies coated on extruded and pelleted core pieces of animal feed would be exposed to air rendering them more subject to oxidation than if the antibodies were in the core itself; (2) the outer layer would be the first to interact

with the digestive processes of the animal, and the antibodies would not be buffered as they would be by elements in the core if the antibodies were in the core. The IgG antibodies are denatured at pH 2, the pH of gastric HCL. Therefore, the gastric HCL which might be rapidly buffered by components in the core material (for example $CaCO_3$), would be expected to attack IgG antibodies in the outer layer more readily; (3) the egg antibodies, already rich in yolk lipid, would be expected to interact with lipid which could interfere with their ability to react with the luminal peptides that regulate food intake. Appendix B describes the process of lipid absorption. In this process, a micelle is formed trapping lipophilic compounds, such as fat soluble vitamins, resulting in their absorption; 4) the post manufacturing handling of pelleted and extruded feeds results in the production of fines which usually are not consumed by animals unless they are forced to do so. Appendix C reports that feed conversion is poorer as the content of fines increased. In pelleted or extruded products, the fines originate from surface material on the core. The surface material of the outer layer would be rich in the egg antibodies. Thus, it would be expected that the antibodies may end up in the feed fines resulting in less consistent exposure in the animal who selected pellets over fines. Even if the animal was forced to consume fines, consistency in exposure to the biologically active antibodies would be minimized; and (5) other reasons that one might expect the applicants' approach to fail to achieve

desirable results are the "insurmountable obstacles" set forth in Appendix A.

12. The teachings of the prior art would lead one skilled in the art away from our invention, because they suggest that particles of an animal feed having an outer layer of fat with antibodies would not be a successful solution to the problem of preserving antibody activity in particulate feed.

13. In the past, the only known way of obtaining the advantages of administering antibodies to animals in their feed was to include the antibodies in a feed mash. As a result, it was not possible to obtain both the advantages of feeding pellets to the animal and administering antibodies to the animal. The animal feed of the present claims solves this problem and makes it possible for the first time to obtain both the advantages of feeding pellets and the advantages of administering antibodies.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001, Title 18, of the U.S.C., and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 6/2/97

Mark E. Cook

Mark E. Cook

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Mark E. Cook et al.
Serial No.:	08/684,785
Filed:	July 22, 1996
Title:	METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN
Art Unit:	1816
Examiner:	F. Pierre VanderVegt

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified patent application.

The fee for that amendment has been calculated as shown below:

CLAIMS AS AMENDED

	Claims After Amendment		Highest Number Paid For Previously	Number Extra	Rate	Additional Fee
Total Claims	5	Minus	20	0 X	$ 22.00	= $.00
Independent Claims	1	Minus	3	0 X	$ 80.00	= $.00
First presentation of a Multiple Dependent Claim					$260.00	= $.00
					Total Fee	$.00

[X] No additional fee is required.

[ ] A check for $ .00 to cover the filing fee and the cost of recording the assignment is enclosed.

[X] Please charge our Deposit Account No. 17-0055 in the amount of $.00. The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Account No. 17-0055. Two extra copies of this sheet are enclosed.

Respectfully submitted,

Dated: June 5, 1997

By: _____
Thad F. Kryshak, Esq.
Registration No. 19,428

Quarles and Brady
411 East Wisconsin Ave.
Milwaukee, WI 53202
(414) 277-5781

MKE\4008244.01

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/684,785	07/22/96	COOK M	960296.94011

18M1/1001

THAD F KRYSHAK
QUARLES & BRADY
411 EAST WISCONSIN AVE
MILWAUKEE WI 53202-4497

EXAMINER	
VANDERVEGT, F	
ART UNIT	**PAPER NUMBER**
1816	7

DATE MAILED: 10/01/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/684,785	Applicant(s) Cook et al
	Examiner F. Pierre VanderVegt	Group Art Unit 1816

☒ Responsive to communication(s) filed on *Jun 9, 1997*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *THREE* month(s), ~~or thirty days, whichever is longer,~~ from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *6-10* ~~is~~/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *6-8 and 10* ~~is~~/are rejected.

☒ Claim(s) *9* is/~~are~~ objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- ***SEE OFFICE ACTION ON THE FOLLOWING PAGES*** ---

DETAILED ACTION

Claims 1-5 have been canceled. New claims 9 and 10 have been added.

Claims 6-10 are currently pending in this application.

1. In view of the amendment and the Declaration of Dr. Mark E. Cook filed June 9, 1997, only the following rejections are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(C) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 6-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,428,072 (E1 on form PTO-1449), in view of U. S. Patent 5,080,895 (D1), Albright et al (U on form PTO-892) and U.S. Patent 3,119,691 (A), all of record.

Applicant's arguments and the Declaration of Dr. Mark E. Cook filed June 9, 1997 have been fully considered but they are not persuasive.

Applicant's argues in the paragraph bridging pages 3-4 of the response and Dr. Cook contends in paragraph 10 of his Declaration that the combination of references supra would result in a product like that of the '691 patent, which dissolves in water. This position would be correct if the Examiner were relying upon the coating material of the '691 patent. However, this is not the case. Applicant's attention is directed to lines 9-11 of page 4 in the Office Action mailed

February 18, 1997, where the relied upon teachings of the '691 patent are stated as "*[t]he '691 patent teaches coating animal food particles by spraying with fat which melts when warmed but solidifies at room temperature (column 4, line 66 through column 5, line 22 in particular). The '691 patent also teaches that said fat may have a powder dispersed in it (column 5, lines 31-37 in particular)*" (emphases added for clarity). The '691 patent, therefore, teaches a method for applying a fat coating to the exterior layer of an extruded food pellet. Applicant's attention is further directed to lines 13-16 of page 4 in the Office Action where the combination of references is explained as "*[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the anti-pathogen antibodies of the '895 patent and the feed conversion enhancing CLA of the '072 patent with the protective fat coating taught by Albright et al and spray the mixture as a coating on an animal feed product*" (emphasis added for clarity). It is clearly evident that the relied upon fat preparation was not the intentionally water-soluble coating of the '691 patent, but, rather, the fat coating of Albright et al with the additional anti-pathogen antibodies of the '895 patent and the feed conversion enhancing CLA of the '072 patent. The '691 patent is clearly relied upon as a means for applying the modified Albright et al coating to the food particles, not as supplying the coating itself. Albright et al clearly teaches that the fat used to encapsulate vitamin A protects its contents from both mineral degradation and hydrolysis (paragraph bridging pages 2035 and 2036 in particular).

Applicant's argues in the first new paragraph in page 4 of the response and Dr. Cook contends in paragraph 6 of his Declaration that the combination of references supra would be presented with "insurmountable obstacles" as referred to on page 104 of Appendix A submitted with the response. Applicant seems to feel that said Appendix A teaches away from the claimed invention in that the fat encapsulated antibodies coated onto the food pellets of the combined references will not work, as they will not be conferred any type of protection from degradation. This position, however, is off point. The cited passage of Appendix A speaks only of "insurmountable obstacles" in regard to vitamins in solution used for coating food pellets. The reference makes no mention, and does not purport to contemplate, vitamins or other additives in a fat coating as taught by the references combined supra. Again, Albright et al specifically teaches

the protective nature of the fat coating of vitamin A (paragraph bridging pages 2035 and 2036 in particular) and further teaches that the fat coating of the vitamin A has a profound effect upon the long-term storability of the product (Table 2 in particular).

Applicant's argues in the first new paragraph in page 5 of the response and Dr. Cook contends in paragraph 11 of his Declaration that the combined references supra would allow the degradation of the encapsulated antibodies in the acidic conditions of the upper gastrointestinal tract. This position is without merit as the '895 patent teaches the feeding of anti-pathogen antibodies isolated from egg yolk to neonatal pigs. The '895 patent antibodies were fed to the pigs in an artificial milk fluid, without any protection against digestive degradation, and the antibodies conferred protection to the pigs against pathogen challenge. Dr. Cook further contends in the same paragraph that the yolk-derived antibodies are rich in lipids which will interfere with the regulation of food intake. This statement is off-point, as the '895 patent clearly teaches that the immunoglobulins can be fractionated from other components of the yolk prior to powdering (column 6, lines 52-65 in particular).

Applicant's argues in the second new paragraph in page 5 of the response and Dr. Cook contends in paragraph 11, section 4, of his Declaration that the combined references supra would be subject to the formation of fines which are unpalatable to livestock and fowl and that the antibodies of the coating would thus be lost and protection of the animals would be inconsistent, citing the teachings presented in Appendix C, submitted with the response, regarding fines. However, the cited reference also clearly states that the amount of fines present in a feed preparation is dependent mainly on the quality of the pellets. The reference also teaches the reduction of fines through the use of binding agents which are well known in the art. One would also reasonably expect that the fat coating on the pellets would also serve, to some extent, as a binding agent, and further that the fat coating would provide a smoother, less abrasive surface to the pellets, tending to reduce the production of fines.

Allowable Subject Matter

3. Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

5. Papers related to this application may be submitted to group 1800 by facsimile transmission. Papers should be faxed to group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1816 is (703)305-3014. *Communications which are not to be entered into the record, such as proposed amendments, should be clearly marked "DRAFT" and faxed to (703)305-7939.*

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Monday through Friday from 8:00 am to 4:30 pm ET. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the group 1800 receptionist, whose telephone number is (703)308-0196.

September 29, 1997
F. Pierre VanderVegt, Ph.D.
Patent Examiner
Art Unit 1816
d8

David A. Saunders
DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 186

Appendix 8

A 1 2 6

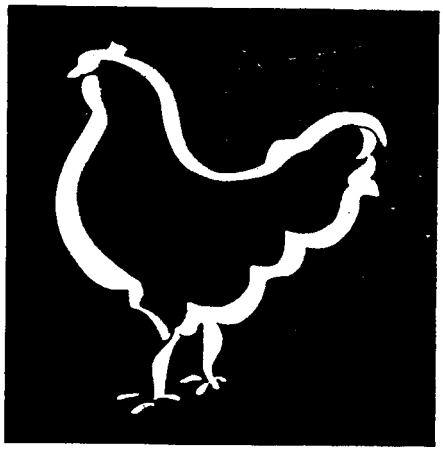
EXHIBIT A

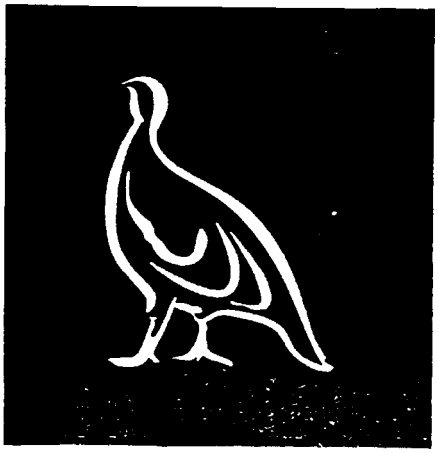
Multi-State Poultry

Feeding and Nutrition Conference

May 25, 1994

BASF Technical Symposium





Animal Nutrition

BASF

VITAMIN STABILITY IN PREMIXES AND FEEDS: A PRACTICAL APPROACH

Mike B. Coelho
Technical Services
Animal Nutrition Department
BASF Corporation
Parsippany, New Jersey

Feed processes tend to improve the distribution of nutrients (premixing) and the digestibility of carbohydrates (pelleting and extrusion). But these processes are harmful to labile nutrients, such as vitamins, that can be easily oxidized (Figure 1) (Gadient, 1986; Schneider, 1986).

Vitamins, as biologically active biochemicals, generally are quite sensitive to their physical and chemical environment. Several vitamins contain unsaturated carbon atoms or have double bonds, both highly susceptible to oxidation. For example, vitamin A retinol has both a free hydroxy group and 5 double bonds (Figure 2). The esterification of retinol with acetic acid produces retinyl acetate which has the hydroxy group protected, but still has 5 double bonds susceptible to oxidation (Figure 3). For this reason, even pure retinyl acetate oil has to be emulsified in gelatin and sugars, and processed into a beadlet containing an antioxidant (Figure 4).

It is critical to calculate the vitamin stability at each stage of processing: premixes, basemixes, pelleting and feed storage, because vitamins incur losses that vary from process to process. Tables 3 through 10 reflect average industry vitamin stability. This data is an average from a broad set of data from vitamin manufacturers' laboratories, industry and academic research, and different conditions of processing and storage.

Vitamin Stress Factors

Several factors can influence vitamin stability during pelleting and storage, including temperature, humidity, conditioning time, reduction and oxidation (redox) reactions and light (Table 1). Heat, pressure, humidity, friction and redox reaction vary drastically among the different ways feed can be processed (Table 2).

n premixes, the dominant effect exerted on vitamins is redox reactions by minerals (Table 5a). Trace minerals also vary in redox potential. Sulfates a higher redox potential than carbonates, and oxides have the lowest re- potential due to lower solubility (Table 6). Friction is also an important or because it erodes the coating that protects several vitamins and reduces min crystals to small pieces. Friction is very high in pelleting (Tables 2 and nd basemixes (Tables 2 and 7).

eting and Extrusion Stress Factors

In eting, the most important factors are friction (abrasion), pressure, , humidity and conditioning time (Tables 2 and 8). Friction and pressure ose more vitamin molecules to chemical destruction. Heat and humidity elerate most chemical reactions. Conditioning time prolongs redox and other mical reactions (Table 8).

In extrusion, the dominant effects are pressure, heat, humidity and redox ctions. Extrusion is also an aggressive process against vitamins due to the h temperatures (250-300F), pressure (400-1000 PSI), and moisture (30%) bles 2, 3 and 9). Expanders seem to be getting a lot of attention in the US rket. They are already in great use in Europe, as a pre-step for pelleting. pander is just another fancy word for high speed extrusion. A large extruder s an 8 inch diameter screw, 200 HP motor and produces 10 ton/hr. A large pander has an 18 inch diameter, 1000 HP motor and produces 60 ton/hr. The ention time and temperature are also lower in expanders. Therefore, expand- s are less stressful to vitamins than extruders (Table 9A).

h eds, the most important factors are humidity and oxidation by polyun- turated fatty acids (PUFA's), peroxides and trace elements. One gram of UFA's destroys 3 IU vitamin E and 3000 IU vitamin A. Vitamin stability in eds (Table 10) does correlate to some extent with vitamin stability in trace ineral premixes (Table 5). However, vitamins tend to be more stable in feeds ersus premixes, since the trace elements and macrominerals are more diluted feeds, and the pellet itself constitutes a barrier to stress factors.

itamins Affected By Pressure

Pressure hardly affects vitamins present as crystalline forms, such as most -vitamins. It can, however, seriously disrupt the coating that protects Vitamin . These sensitive vitamins are designed with a chemical protection consisting f an antioxidant and a physical protection of a coating. The coating frequently s a gelatin-starch based matrix.

Molecular Stability

In fat soluble vitamins, esters are significantly more stable than alcoh The hydroxy group of alcohols is extremely sensitive to oxidation. The double bonds in retinyl acetate still make the compound sensitive to oxi tions. Vitamin A is significantly more stable in vitamin premixes than in v min-trace mineral premixes because trace minerals catalyze oxidation of five double bonds (Tables 3, 4 and 5a,b). Christian, 1983, determined the bility of Vitamin A in a basemix. After 3 months storage, the Vitamin A ret tion was 88% under low temperature and humidity, 86% under high tempe ture and low humidity and 2% under high temperature and high humidity. T concluded that humidity was significantly more stressful than temperatu Shields et al., 1982, measured the stability of Vitamin A in mash and pellet feeds. After 3 months storage, vitamin A retention varied from 50% at l temperature to 39% at high temperature in mash feed and 65% at low tempe ture and 20% at high temperature in pelleted feeds.

New Technology Provides Significant Improvement

New technology has further improved Vitamin A stability by a crosslinki process, such as the reaction between the gelatin and the sugar, that makes t beadlet insoluble in water, giving it a more resistant coating that can susta higher pressure, friction, temperature and humidity (Figure 4).

Stability studies conducted with new crosslinked Vitamin A indicate high stability than with soluble beadlets. Chen, 1990, measured the stability of the crosslinked Vitamin A beadlets on the market in trace mineral premixes an feeds. After 3 months storage at high temperature and humidity, the Vitamin retention varied from 30 to 80%, depending on the antioxidant present in th beadlet. In a 30% dairy concentrate pelleted at 200°F, retention at pelletin varied from 78 to 96%. After 3 months storage at high temperature and humic ity, retention varied between 57 and 62%. The improvements in Vitamin stability through extrusion, in the last decade, increased by 35% mainly due t the use of crosslinking processes.

Vitamin E and Minerals

Vitamin E, as d,l-alpha-tocopherol, is an antioxidant by itself and, there fore, if applied directly to feeds, is consumed rapidly. The free phenolic hy droxy group in this molecule is responsible for the antioxidant activity (Figur 5). When the hydroxy group is protected by formation of an ester, as in tocophery acetate, the compound obtained is resistant to oxygen, since it has no double

nds and free hydroxy groups (Figure 6). Vitamin E acetate is stable in feeds
th neutral or slightly acidic pH. However, even slightly alkaline conditions
y affect the stability, such as when limestone carrier is used or in the pres-
ce of large quantities of magnesium oxide (Basemixes). Under these condi-
ns, some of the protective acetate groups split off and free tocopherol is
rmed, which can be rapidly oxidized. Dove and Ewan, 1986, determined the
ibility of alpha-tocopherol in feeds without and with trace minerals. At the
d of 3 months storage at 25-30 C, alpha-tocopherol retention was 50% and
%, respectively. The further addition of 245 ppm copper as copper sulfate,
oduced 0% retention after 15 days. Tocopherol, the most concentrated form
V in E activity, is such an unstable vitamin form that it should not be
nsidered for any animal nutrition application.

Schneider, 1988, determined the stability of tocopheryl acetate and toco-
erol in vitamin-trace mineral premixes stored at ambient and stressful condi-
ons. At the end of 1 month storage at ambient conditions, the retention was
5% and 44%, respectively, and at high temperature and humidity, the reten-
on was 90% and 13%, respectively.

Menadione, pure vitamin K_3, is a crystalline yellow powder that is unstable
nd irritating to skin and mucous membranes. It is not utilized in pure form, but
formulated with sodium bisulfite and derivatives thereof. Menadione sodium
isulfite complex (MSBC) and Menadione dimethyl pyrimidinol bisulfate
MPB) are more stable than MSB.

B-Vitamins Stability

Vitamins are also unstable to a certain extent. Vitamin B_1 and B_6 are
nore stable under acidic conditions, while pantothenic and folic acids are most
table in a slightly alkaline environment. pH of the medium is far less impor-
ant than the aggressiveness of moisture and trace elements. Thiamine hydro-
chloride is destroyed rapidly in a choline/trace mineral premix (high moisture,
pH 4-5) while it is fairly stable in a basemix (low moisture, pH 7-8). Vitamin
solubility in water is inversely correlated to stability (Table 14). Thiamine
mononitrate with a solubility of 10g/100ml, is significantly more stable in
premixes than thiamine hydrochloride with a solubility of 100 g/100 ml (Adams,
1982) (Figure 7).

Vitamin B_6 is more rapidly destroyed in a choline chloride/trace mineral
premix (high moisture) than in a basemix (low moisture). Calcium-d-pantoth-
enate is quite stable. Losses occur only after prolonged storage at acidic pH.

Riboflavin is stable in all premixes and also under climatic stress.

Vitamin B_{12} and choline are very stable compounds, but B_{12} is slightl
sitive to strong acid, alkali, reduction, light, ascorbic acid and ferrous s

Folic acid is stable to heat and air, but unstable in acid and alkalin
tions. It is light sensitive, slightly sensitive to moisture and sensitive to
tion and reducing agents.

Vitamin C, as ascorbic acid, is extremely difficult to maintain in pre
or feeds since it is susceptible to destruction by so many environmental fa
especially oxidation. Phosphorilation of ascorbic acid (Ascorbyl phos
produces a highly stable product.

Zhuge and Klopfenstein, 1985, determined the stability of riboflavi
niacin in a broiler premix without and with trace minerals. At the end
months storage, riboflavin retained 50% and 46%, respectively. Niacin ret
96% and 91%, respectively. Schaaf, 1990, reported retentions of 100%,
and 93% for pyridoxine, riboflavin and folic acid, respectively, in vit
premixes stored at ambient temperature for 3 months. Christian, 1983,
basemix study, determined riboflavin and calcium pantothenate stability a
months storage. Riboflavin retained 72% at low temperature and humidity
35% at high temperature and humidity. Calcium pantothenate retained
and 16%, respectively. Adams, 1982, reported the stability of pyridoxin
thiamine in premixes without and with trace minerals. After storage for 3 m
under stressful conditions, pyridoxine retained 100% and 45%, respecti
After 21 days under stressful conditions, thiamine hydrochloride retained
and thiamine mononitrate, 95%. BASF, 1986, compared the stability of
talline ascorbic acid and ethyl cellulose coated ascorbic acid through pelle
Crystalline retained 85% and ethyl cellulose, 82%. A follow up study d
mined the stability of ascorbyl-phosphate. This compound not only is very st
but also maintains the bioavailability. Ascorbyl phosphate retained 95% thr
extrusion (Figure 8).

Practical Applications

The vitamin stability data presented in Tables 4 through 10 follow the
eral steps used in feed manufacturing. Based on specific conditions, one
calculate exactly each vitamin retention from time of purchasing, until
absorbed by the animal. Tables 11, 12 and 13 consolidate the data for spe
management conditions. In each case, the vitamin retentions for each manu
turing step are multiplied, producing the total vitamin retention from tim
purchasing to time of feeding. The continued increase in pelleting tempera

and conditioning time is destroying vitamins at a much higher rate. Since 1980, the average pelleting temperature in broiler feed mills has increased from 160°F to as high as 210°F. Vitamin supplementation needs to be adjusted accordingly to offset these higher losses.

Vitamin Application After Pelleting

The high losses experienced by some vitamins through pelleting has led to a constant search for ways to reduce these losses. The option most commonly proposed is vitamin application after pelleting and extrusion. No matter how ca l the application (usually spraying), it presents insurmountable obstacles. (1)Difficulty in maintaining vitamins in solution. (2)Vitamin forms in a liquid medium have no protection. (3)Vitamin solutions will only coat the outside of the pellet (spraying hot pellets does increase penetration but will also increase vitamin losses). (4)The vitamin distribution throughout the feed is very poor, with a coefficient variation, c.v., of 20-50%, which is unacceptable for small to medium size animals (poultry and swine). Poor distribution of nutrients leads to variable performance throughout a flock. (5)Storage time of 2 to 6 weeks for vitamin-coated feed will lead to very high vitamin losses, since these vitamins will be overly exposed to environmental stresses.

REFERENCES

Adams, C.R., 1982. Folic acid, thiamine and pyridoxine. Vitamins - The Life Essentials. National Feed Ingredient Institute. NFIA. Ames, Iowa.

BASF, 1986. Effect of pelleting on crystal and ethyl cellulose-coated ascorbic acid assay levels of poultry feed. BASF Animal Nutrition Research. RA873.

Chen, J., 1990. Technical Service Internal Reports. BASF Corporation, Wyandotte, Michigan.

Christian, L.D., 1983. Vitamin stability in mineral mixes formulated with different calcium phosphates stored at two temperatures and relative humidities. Proceedings AFIA Nutrition Council. p. 22.

Dove, C.R. and R.C. Ewan, 1986. The effect of diet composition on the stability of natural and supplemental vitamin E. Swine Research Report AS-580-J. Iowa State University. Ames, Iowa.

Gadient, M. 1986. Effect of pelleting on nutritional quality of feed. M. Nutrition Conference. p. 73.

Schaaf, R.L., 1990. Quality Assurance Internal Reports. BASF Corp Wyandotte, Michigan.

Schneider, J., 1986. Synthesis; formulation and stability of vitamins. P ings of the Twenty-second Annual Nutrition Conference for Feed facturers. p. 18.

Schneider, J., 1988. Technical service internal reports, BASF AG Anim trition, Ludwigshafen, Germany.

Shields, R.G., D.R. Campbell, D.M. Hughes and D.A. Dillingham. 198 searchers study vitamin A stability in feeds. Feedstuffs. Nov. 15, p.

Zhuge, Q. and C.F. Klopfenstein. 1986. Factors affecting storage stabi vitamin A, riboflavin and niacin in a broiler diet premix. Poult. Sci. 6:

Vitamin	Moisture	Oxidation	Reduction	Trace Minerals	Heat	Light	pH Acid	pH Neutral	pH Basic
A (beadlet)	S	S	R	S	MS	MS	S	R	R
D (beadlet)	S	S	R	S	MS	MS	S	R	R
E (acetate)	R	R	R	MS	R	R	MS	R	S
K (mpb, msbc)	VS	R	MS	VS	MS	S	MS	R	S
Thiamine HCL	S	S	S	MS	S	R	R	MS	S
Thiamine Mono	R	MS	MS	MS	MS	R	R	MS	S
Riboflavin	R	R	MS	R	R	MS	R	MS	S
Pyridoxine	R	R	R	MS	R	S	R	MS	S
B_{12}	R	MS	S	MS	MS	S	MS	R	MS
Calcium Pantothenate	S	R	R	R	MS	R	S	MS	R
Folic Acid	R	MS	MS	S	MS	MS	S	R	MS
Biotin	R	R	R	R	S	R	MS	R	R
Niacin	R	R	R	R	R	R	R	R	R
Niacinamide	S	R	R	R	R	R	MS	R	MS
C	R	VS	R	VS	R	MS	R	R	S
Choline Chloride	VS	R	R	R	R	R	R	R	MS

R = RESISTANT
MS = MILDLY SENSITIVE
S = SENSITIVE
VS = VERY SENSITIVE

106

Table 2. Level of Vitamin Stress in Different Feed Processes

	Vitamin Premix	Choline/ Trace Mineral Premix	Basemixes	Pelleting	Extrusion, Expandin
Heat	low	low	low	high	very high
Pressure	low	low	low	high	very high
Humidity	low	high	low	high	very high
Redox reactions	low	high	high	high	very high
Friction	low	high	high	very high	low

Table 3. Vitamin Stability in Premixes, Pelleting and Extrusion

Vitamin	STABILITY				
	Very High	High	Moderate	Low	Very Lo
	choline chloride B_{12} pantothenic acid	riboflavin niacin pyridoxine E biotin	thiamine mono folic acid D_3 A	thiamine hcl	menadi ascorbi

	LOSSES/MONTH				
• premixes without choline and trace minerals	0%	<0.5%	0.5%	1%	2%
• premixes with choline	<0.5%	2%	3%	6%	10%
• premixes with choline and trace minerals	2%	6%	9%	15%	30%
• pelleting	3%	8%	11%	16%	50%
• extrusion	4%	15%	18%	25%	80%

107

VITAMIN	VITAMIN RETENTION % MONTH 0.25	0.5	1	2	3	4	5	6	% Avg. Loss/Month
A 650 Beadlet	100	99	99	98	97	96	95	94	1.0
D_3 325 Beadlet	100	99	99	98	98	97	97	96	0.6
D_3 400 M.S.	100	99	99	98	97	96	95	94	1.0
E Acetate 50%	100	99	99	98	98	98	98	98	0.2
E Alcohol	90	80	64	36	21	13	7	0	35.0
MSBC	100	99	98	97	96	94	92	90	1.8
MPB	100	99	98	97	96	95	94	92	1.2
Thiamine HCL	100	99	99	98	97	96	95	94	0.7
Thiamine Mono	100	99	99	99	99	98	98	97	0.4
Riboflavin	100	99	99	99	99	99	99	98	0.3
Pyridoxine	100	99	99	99	98	98	98	97	0.4
B_{12}	100	100	100	100	100	99	99	99	0.2
Calc Pantothenate	100	99	99	99	99	98	98	98	0.3
Folic Acid	100	99	99	99	99	98	98	97	0.4
Biotin	100	99	99	99	99	98	98	98	0.3
Niacin	100	99	99	99	99	98	98	98	0.3
Niacinamide	100	99	99	98	97	96	96	96	0.4
Ascorbic Acid	98	96	88	83	78	73	69	65	6.6
Coated Ascorbic	99	97	89	85	80	75	72	68	6.3
Ascorbyl Phosphate	100	99	99	98	98	97	97	96	0.6

108

Table 4A. Average Industry Vitamin Stability in Vitamin (w/Choline) Premixes

VITAMIN	VITAMIN RETENTION % MONTH 0.25	0.5	1	2	3	4	5	6	% Avg. Loss/Month
A 650 beadlet	99	98	97	96	94	93	91	89	2.2
D_3 325 beadlet	100	99	98	97	96	95	94	92	1.2
D_3 400 M.S.	99	98	96	95	93	92	90	89	2.2
E acetate 50%	100	100	99	99	99	98	98	97	0.4
E alcohol	89	77	52	30	18	10	5	1	40.0
MSBC	95	93	84	73	65	59	53	48	10.0
MPB	98	96	87	75	68	62	57	52	9.0
Thiamine HCL	99	97	89	83	78	75	71	68	7.1
Thiamine Mono	99	98	95	92	89	85	83	80	3.5
Riboflavin	100	99	98	95	92	89	85	82	2.9
Pyridoxine	99	98	95	92	89	85	83	80	3.5
B_{12}	100	100	99	99	99	98	98	97	0.4
Calc Pantothenate	100	99	98	95	92	89	85	82	2.9
Folic Acid	98	96	95	90	86	82	78	75	4.2
Biotin	100	99	98	95	92	89	85	82	2.9
Niacin	100	99	98	96	92	90	85	81	2.9
Niacinamide	98	96	95	92	88	86	81	77	3.9
Ascorbic Acid	93	88	73	61	57	49	39	31	15.0
Coated Ascorbic	95	90	76	64	60	53	44	36	12.0
Ascorbyl Phosphate	100	99	98	97	96	95	94	92	1.2
Choline	100	100	99	99	99	99	98	98	0.2

109

VITAMIN	VITAMIN RETENTION % MONTH 0.25	0.5	1	2	3	4	5	6	% Avg. Loss/Month
A 650 beadlet	98	96	94	90	84	79	75	70	5.0
D_3 325 beadlet	99	98	96	92	88	85	81	77	4.0
D_3 400 M.S.	98	96	91	86	77	73	69	65	6.0
E acetate 50%	99	98	96	95	93	90	87	84	2.7
E alcohol	90	78	50	28	14	7	4	0	46.0
MSBC	95	82	65	57	48	39	29	20	25.0
MPB	95	86	67	58	49	41	31	24	22.0
Thiamine HCL	97	94	86	74	64	55	50	42	12.0
Thiamine Mono	99	98	92	85	80	74	68	65	6.0
Riboflavin	99	98	95	88	82	78	73	71	5.0
Pyridoxine	99	97	94	87	82	76	70	66	5.6
B_{12}	100	99	97	95	94	93	92	90	1.4
Calc Pantothenate	99	97	95	88	83	77	71	69	5.3
Folic Acid	98	96	85	80	74	68	63	58	8.0
Biotin	99	97	94	87	82	76	70	66	5.5
Niacin	99	97	95	88	83	77	71	69	5.3
Niacinamide	99	95	91	84	79	71	67	64	6.1
Ascorbic Acid	90	76	64	54	44	34	24	15	30.0
Coated Ascorbic	92	78	64	56	47	37	28	19	28.0
Ascorbyl Phosphate	99	98	96	92	88	85	81	77	4.0

110

[redacted]

Table 5A. Average Industry Vitamin Stability in Vitamin (W/ Choline) Trace Mineral Premixes

111

VITAMIN	VITAMIN RETENTION % MONTH 0.25	0.5	1	2	3	4	5	6	% Avg. Loss/Month
A 650 Beadlet	97	95	85	80	74	68	63	58	8.0
D_3 325 Beadlet	98	96	91	86	77	73	69	65	6.0
D_3 400 M.S.	97	95	85	80	72	62	56	50	9.5
E Acetate 50%	98	97	95	93	91	88	85	82	3.1
E Alcohol	85	78	35	20	7	0	0	0	57.0
MSBC	90	80	64	36	21	13	7	0	38.0
MPB	91	81	65	38	23	16	11	0	34.0
Thiamine HCL	92	86	70	58	53	45	35	27	17.0
Thiamine Mono	98	96	90	79	72	64	59	52	9.6
Riboflavin	99	97	95	85	78	70	65	59	8.2
Pyridoxine	97	95	92	83	76	67	62	56	8.8
B_{12}	100	99	98	97	95	93	91	89	2.2
Calc Pantothenate	99	97	95	86	79	70	65	58	8.4
Folic Acid	97	93	85	73	63	56	50	43	12.2
Biotin	98	96	93	84	77	68	63	57	8.6
Niacin	99	97	95	86	79	70	65	58	8.4
Niacinamide	99	96	92	82	74	64	60	52	9.6
Ascorbic Acid	90	80	60	36	22	13	8	0	40.0
Coated Ascorbic	92	82	63	39	25	17	12	4	32.0
Ascorbyl Phosphate	98	96	91	86	77	73	69	65	6.0
Choline chloride	100	00							

Table 6. Effect of Trace Element Source

VITAMIN	TRACE ELEMENT SOURCE	VITAMIN RETENTION % MONTH 0.5	1	2	3	4	5	6	% Avg. Loss/Month
A 650 Beadlet	oxide	96	92	87	82	78	73	71	5.0
	carbonate	95	89	83	89	70	66	62	7.0
	sulfate	93	86	74	65	57	53	47	11.0
E Acetate 50%	oxide	98	96	95	94	92	90	88	2.3
	carbonate	98	96	95	93	91	89	87	2.4
	sulfate	97	95	92	88	86	83	80	3.0
MSBC	oxide	86	68	59	50	42	32	25	20.0
	carbonate	82	66	57	48	39	29	20	25.0
	sulfate	75	55	30	20	10	5	0	45.0
Thiamine Mono	oxide	97	91	82	75	68	63	56	8.0
	carbonate	96	90	79	72	64	59	52	9.0
	sulfate	94	86	74	64	55	50	42	12.0
Biotin	oxide	97	96	88	82	74	68	65	6.0
	carbonate	97	95	87	80	70	64	61	7.0
	sulfate	95	88	76	66	58	53	47	11.0

112

Table 7. Average Industry Vitamin Stability in Basemixes (W/ Choline and Magnesium)

VITAMIN	VITAMIN RETENTION % MONTH 0.25	0.5	1	2	3	4	5	6	% Avg. Loss/Month
A 650 Beadlet	98	96	92	86	82	78	73	70	5.0
D_3 325 Beadlet	99	98	95	92	88	86	83	80	3.3
D_3 400 M.S.	96	96	92	86	82	78	73	71	5.0
E Acetate 50%	99	98	94	89	86	81	77	73	4.5
E Alcohol	85	70	30	10	5	0	0	0	70.0
MSBC	90	80	64	36	22	13	7	0	38.0
MPB	91	81	65	38	23	16	11	0	34.0
Thiamine HCL	97	93	85	73	63	56	50	43	12.2
Thiamine Mono	98	96	90	79	72	64	59	52	9.6
Riboflavin	99	97	95	85	78	70	65	59	8.2
Pyridoxine	98	96	93	86	78	69	64	61	8.0
B_{12}	100	99	98	97	95	93	91	89	2.2
Calc Pantothenate	99	98	97	88	83	77	72	65	7.0
Folic Acid	97	93	86	74	65	57	53	47	11.0
Biotin	99	97	95	87	80	70	64	61	8.0
Niacin	99	98	96	88	80	74	68	61	7.8
Niacinamide	98	97	95	86	77	70	63	55	9.0
Ascorbic Acid	88	75	53	27	16	7	2	0	50.0
Coated Ascorbic	90	77	56	30	19	11	6	0	40.0
Ascorbyl Phosphate	99	98	95	92	88	86	83	80	3.3
Choline Chloride	100	99							

113

VITAMIN	Pelleting Temperature, F / Conditioning Time, Min.								
	140/2 150/1 160/0.5 170/0.3	150/2 160/1 170/0.5 180/0.3	160/7 170/1 180/0.5 190/0.3	170/2 180/1 190/0.5 200/0.3	180/2 190/1 200/0.5 210/0.3	190/2 200/1 210/0.5 220/0.3	2[illegible] 220/0.5 230/0.3	210/2 220/1 230/0.5	220/2 230/1
A 650 Beadlet	96	94	93	92	90	88	85	82	79
D_3 325 Beadlet	97	96	95	94	93	92	91	90	89
D_3 400 M.S.	96	94	92	91	88	86	82	80	77
E Acetate 50%	97	96	95	94	93	92	91	90	88
E Alcohol	75	70	65	60	54	48	43	39	23
MSBC	80	76	72	70	65	60	56	51	44
MPB	82	78	74	73	68	64	60	57	50
Thiamine HCL	93	91	89	86	82	78	74	68	63
Thiamine Mono	96	94	93	90	89	87	84	80	77
Riboflavin	96	94	93	91	89	87	84	80	78
Pyridoxine	94	93	92	90	87	85	82	78	75
B_{12}	99	98	97	97	96	96	95	95	94
Calc Pantothenate	95	94	93	91	89	87	84	80	78
Folic Acid	95	94	93	90	89	87	84	80	77
Biotin	95	94	93	90	89	87	84	80	77
Niacin	96	95	94	91	90	89	86	82	80
Niacinamide	94	93	91	88	87	85	81	78	77
Ascorbic Acid	65	60	55	50	45	40	35	30	25
Coated Ascorbic	67	62	57	53	47	44	39	34	30
Ascorbyl Phosphate	97	96	95	94	93	92	91	90	89
Choline Chloride	99	99	98	98	97	97	96	96	95

104

Table 9. Average Industry Vitamin Stability Through Extrusion

VITAMIN	VITAMIN RETENTION % Extrusion Temperature F / Barrel Retention Time, Min.										
	230/2 240/1 250/0.5 260/0.3	240/2 250/1 260/0.5 270/0.3	250/2 260/1 270/0.5 280/0.3	260/2 270/1 280/0.5 290/0.3	270/2 280/1 290/0.5 300/0.3	280/2 290/1 300/0.5 310/0.3	290/2 300/1 310/0.5 320/0.3	300/2 310/1 320/0.5 330/0.3	310/2 320/1 330/0.5 340/0.3	320/2 330/1 340/0.5 350/0.3	3302 340/2 350/0.5 360/0.3
A 650 Beadlet	93	92	91	90	88	86	83	80	77	74	71
D_3 325 Beadlet	95	95	94	93	92	91	89	87	85	84	83
D_3 400 M.S.	90	90	89	85	82	78	74	70	66	62	57
E Acetate 50%	95	94	93	92	91	90	88	86	84	83	81
E Alcohol	65	60	55	50	45	39	33	22	15	10	5
MSBC	70	65	60	55	50	45	40	35	30	25	20
MPB	72	67	63	57	54	47	44	37	33	29	26
Thiamine HCL	90	88	85	82	79	75	70	65	60	55	50
Thiamine Mono	94	92	90	88	86	84	83	81	80	79	77
Riboflavin	92	90	88	86	84	82	80	77	74	73	68
Pyridoxine	93	92	90	88	86	85	84	81	79	78	73
B_{12}	97	96	95	94	93	92	91	90	89	87	86
Calc Pantothenate	94	93	91	89	87	86	85	83	81	79	76
Folic Acid	93	92	90	88	86	77	76	71	70	67	64
Biotin	93	92	90	88	86	77	76	72	69	66	63
Niacin	92	91	89	87	85	77	76	72	70	68	64
Niacinamide	90	88	87	85	83	74	73	70	67	65	62
Ascorbic Acid	57	53	47	42	37	31	25	20	15	10	5
Coated Ascorbic	59	55	49	45	40	34	29	25	21	15	10
Ascorbyl Phosphate	96	95	94	93	92	91					

105

Table 9A. Average Industry Vitamin Stability Through Expanders

VITAMIN	VITAMIN RETENTION % — Expander Temperature F / Barrel Retention Time, Sec.										
	200/30 210/20 220/10 230/5	210/30 220/20 230/10 240/5	220/30 230/20 240/10 250/5	230/30 240/20 250/10 260/5	240/30 250/20 260/10 270/5	250/30 260/20 270/10 280/5	260/30 270/20 280/10 290/5	270/30 280/20 290/10 300/5	280/30 290/20 300/10 310/5	290/30 300/20 310/10 320/5	300/30 310/20 320/10 330/5
A 650 Beadlet	98	97	96	95	94	92	90	87	84	82	79
D_3 325 Beadlet	99	98	98	97	96	96	96	93	91	89	88
D_3 400 M.S.	94	93	93	92	88	85	82	78	74	70	68
E Acetate 50%	99	98	97	96	96	96	94	92	90	88	87
E Alcohol	75	70	85	80	55	50	45	39	33	22	15
MSBC	80	75	70	65	60	58	50	45	40	35	30
MPB	83	78	73	68	64	59	54	50	45	40	35
Thiamine HCL	94	92	91	88	85	82	78	73	68	63	58
Thiamine Mono	99	97	96	94	91	89	86	85	83	82	81
Riboflavin	95	94	92	90	88	86	84	82	79	78	75
Pyridoxine	96	95	94	92	90	88	87	86	83	81	80
B_{12}	99	98	97	97	96	95	95	94	93	91	90
Calc Pantothenate	97	96	95	93	91	89	88	87	85	83	81
Folic Acid	96	95	94	92	90	88	79	78	73	72	69
Biotin	96	95	94	92	90	88	79	78	74	71	68
Niacin	95	94	93	91	89	87	79	78	74	72	70
Niacinamide	93	92	90	89	86	84	75	74	70	68	66
Ascorbic Acid	69	64	60	54	50	46	39	33	28	23	18
Coated Ascorbic	71	66	62	58	52	48	41	35	30	25	20
Ascorbyl Phosphate	99	98	98	97	96	95	94	93	90	88	87
Choline Chloride	100	100	99	99	98	98	98	97	97	97	96

Table 10. Average Industry Vitamin Stability in Feeds

VITAMIN	VITAMIN RETENTION % — MONTH								% Avg. Loss/Month
	0.25	0.5	1	2	3	4	5	6	
A 650 Beadlet	96	92	83	76	69	60	51	43	9.5
D_3 325 Beadlet	97	93	88	84	78	72	65	58	7.5
D_3 400 M.S.	97	92	84	75	60	54	50	40	12.0
E Acetate 50%	99	98	96	94	92	91	89	88	2.0
E Alcohol	90	78	59	33	20	11	5	0	40.0
MSBC	93	85	75	61	52	44	37	32	17.0
MPB	94	86	76	63	54	47	40	37	15.0
Thiamine HCL	97	93	86	74	65	57	53	47	11.0
Thiamine Mono	99	98	97	88	83	77	72	65	5.0
Riboflavin	99	97	93	92	88	86	84	82	3.0
Pyridoxine	97	95	91	87	84	81	78	76	4.0
B_{12}	99	98	97	96	95	94	93	92	1.4
Calc Pantothenate	99	98	94	93	90	88	87	86	2.4
Folic Acid	99	98	97	88	83	77	72	65	5.0
Biotin	97	95	90	86	82	78	76	74	4.4
Niacin	96	93	88	84	80	76	74	72	4.6
Niacinamide	96	91	86	81	77	72	70	68	4.9
Ascorbic Acid	90	80	64	45	31	22	15	7	37.0
Coated Ascorbic	92	82	67	48	35	27	20	13	30.0
Ascorbyl Phosphate	96	93	88	84	78	72	[illegible]	[illegible]	

Table 11. Integrated Broiler

	1	2	3	4
	Vitamin Premix Storage Time (TABLE 4)	Pelleting Temperature/ Conditioning Time (TABLE 7)	Feed Storage Time (TABLE 10)	Total Vitamin Retention % 1x2x3
	1 Month	200°F 0.5 min.	2 Week	
VITAMIN	% RETENTION			
A 650 Beadlet	99	90	92	82
D_3 325 Beadlet	99	93	93	86
E Acetate 50%	99	93	98	90
MSBC	98	65	85	54
Thiamine	99	89	98	86
Riboflavin	99	89	97	85
Pyridoxine	99	87	95	82
B_{12}	100	96	98	94
C-Pantothenate	99	89	98	86
Folic Acid	99	89	98	86
Biotin	99	89	95	84
Niacin	99	90	93	83

Table 12. Integrated Broiler with Expander

	1	2	3	4	5
	Vitamin Premix Storage Time (TABLE 4)	Expander Temperature Retention Time (TABLE 9A)	Pelleting Temperature/ Conditioning Time (TABLE 7)	Feed Storage Time (TABLE 10)	Total Vitamin Retention % 1x2x3x4
	1 Month	250° F 10 Sec.	200° F 0.5 min.	2 Week	
VITAMIN		% RETENTION			
A 650 Beadlet	99	95	90	92	78
D_3 325 Beadlet	99	97	93	93	83
E Acetate 50%	99	96	93	98	87
MSBC	98	65	65	85	35
Thiamine	99	94	89	98	81
Riboflavin	99	90	89	97	77
Pyridoxine	99	92	87	95	75
B_{12}	100	97	96	98	91
C-Pantothenate	99	93	89	98	80
Folic Acid	99	92	89	98	79
Biotin	99	92	89	95	77
Niacin	99	91	90	93	76

	1	2	3	4
	min Trace Mineral Premix (TABLE 5)	Pelleting Temperature/ Conditioning Time (TABLE 7)	Feed Storage Time (TABLE 10)	Total Vitamin Retention %
	2 Months	180° 1 min.	1 Month	1x2x3
VITAMIN	% RETENTION			
A 650 Beadlet	80	90	83	60
D_3 325 Beadlet	88	93	88	70
E Acetate 50%	95	97	96	88
MSBC	38	85	75	18
Thiamine Mono	79	89	97	68
Riboflavin	85	89	93	70
Pyridoxine	83	87	91	66
B_{12}	97	96	97	90
C-Pantothenate	86	89	94	72
Folic Acid	73	89	97	63
Biotin	84	89	90	67
Niacin	86	90	88	68

Table 14. Physical Properties of Commercial Vitamins

Vitamin	Formulation	Appearance	Color	In Water g/100 ml	pH 1g/100ml
Thiamine	Mononitrate	Crystalline Powder	White	10	6-7.5
Thiamine	HCl	Crystalline Powder	White	100	2.5-3.5
Niacin	Niacin	Crystalline Powder	White	1-2	2-3.5
Niacinamide	Niacinamide	Crystalline Powder	White	69	6-8
K	MSBC	Powder	White-Yellow	40	7
K	MPB	Powder	Grey-Brown	10	3.5-4.5

ure 1

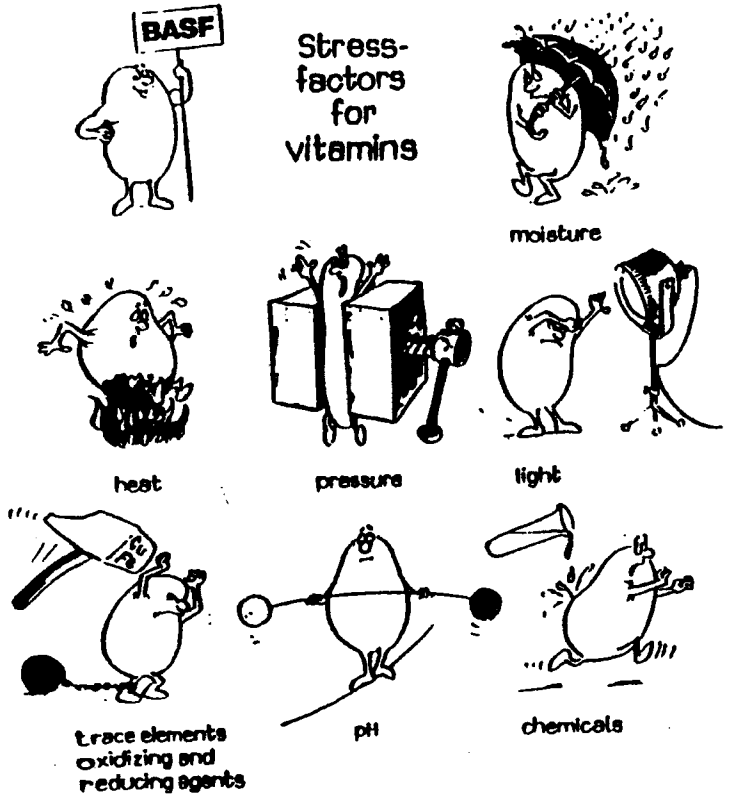
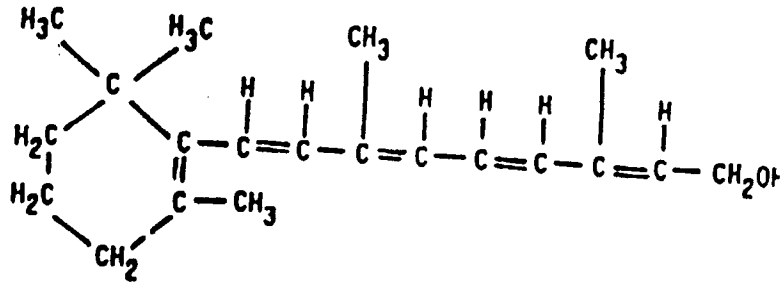
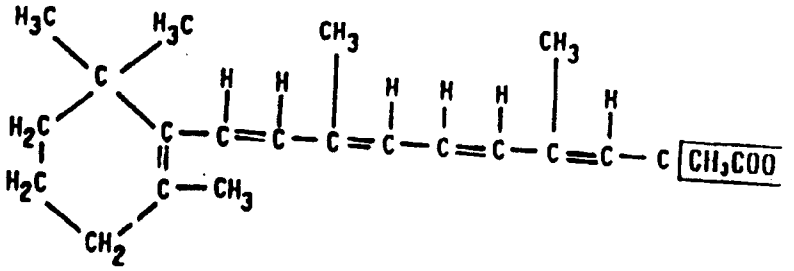


Figure 2



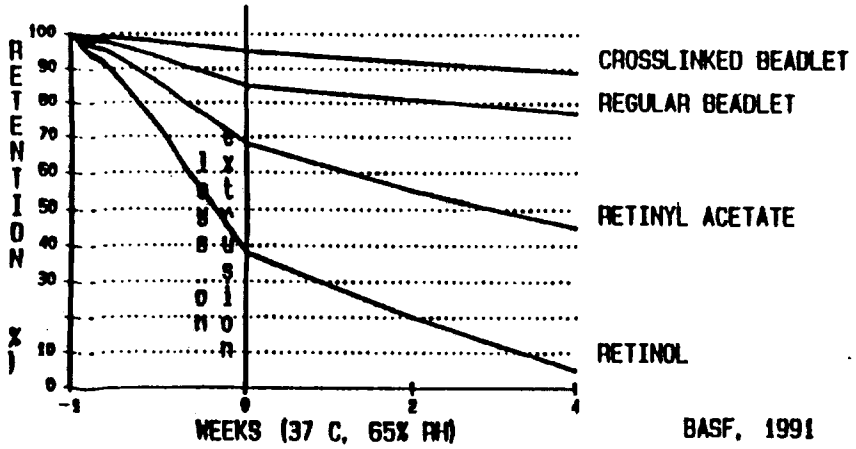
The structure of vitamin A (retinol).

Figure 3



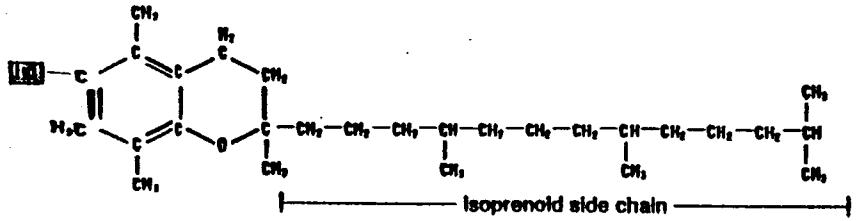
The structure of vitamin A acetate.

Figure 4



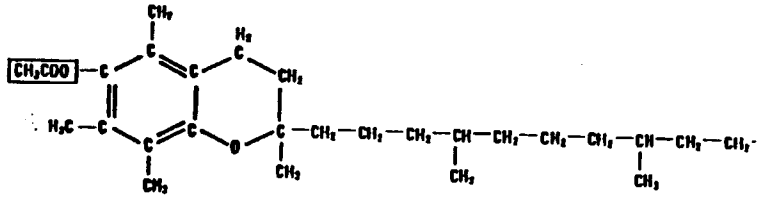
Stability of Vitamin A on Extrusion

Figure 5



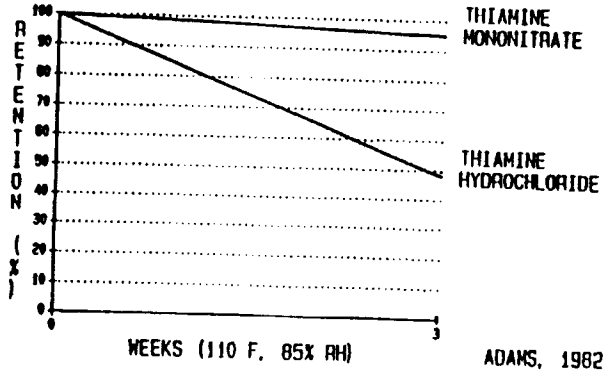
Structure of Alpha-Tocopherol

Figure 6



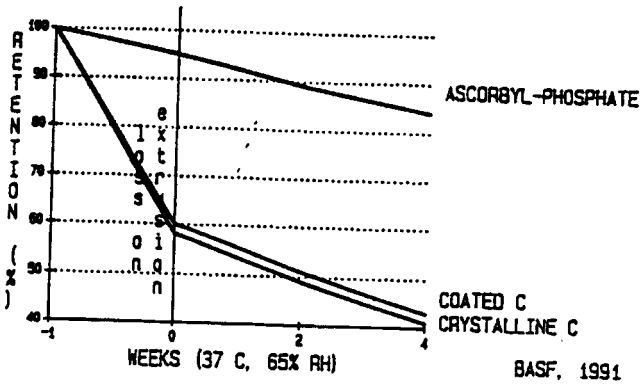
Structure of Alpha-Tocopheryl Acetate
Tocopheryl acetate is synthesized by esterification of α-tocopherol with acetic acid.

Figure 7



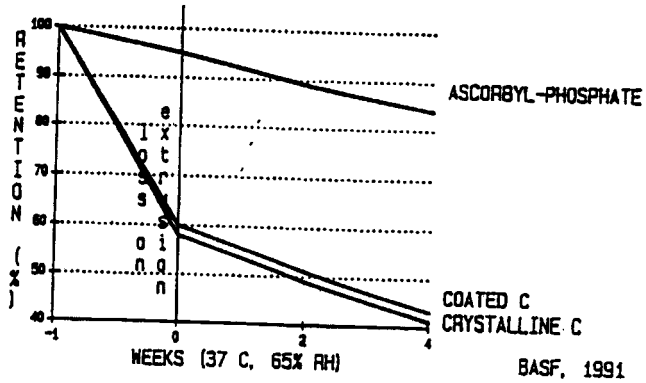
Storage Stability of Thiamine in a Vit-T.M. Premix

Figure 8



Stability of Ascorbic Acid on Extrusion at major catfish feed manufacturer

Figure 8



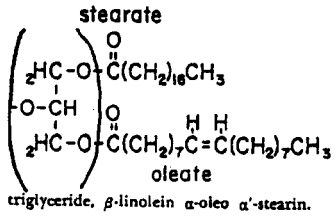
Stability of Ascorbic Acid on Extrusion at major catfish feed manufacturer

:RGY

hich are derived by hydrolysis from
) alcohols, such as glycerol, cetanol
cholesterol, ergosterol and sitosterol.

r, of all lipids only linoleic acid is
n. The importance of linoleic acid
egg production and egg size will be
book. All other lipids are important
"solvents" which aid in absorption
rials which reduce the dustiness of
he passage of feeds through pellet
ty of some feeds. Of these properties,
ar most important.

ipids. Fats and oils. The empirical
$)_9$). The chemical structure of such
ed with glucose, with an empirical
many times more carbon and hydro-
ntent (in fat, C:O = 8.5:1; H:O =



triglyceride, β-linolein α-oleo α'-stearin.

: 2:1). Thus, fat contains a large ex-
of being burned to CO_2 and H_2O.
, is considerably higher per unit
ose or other carbohydrates.
he gross energy value of pure fats
r gram, approximately 2.25 times
y value of approximately 4.15 kilo-

umber of common fats and oils is
f the common fatty acids found in
2.

ats. The digestibility of fats and
lepending upon many factors. The
ompromise between the hydrolytic

Table 2.1. FATTY ACID COMPOSITION AND SOME PHYSICAL PROPERTIES OF A FEW COMMON FATS AND OILS

	Titre °C	*Iodine value*	*12:0*	*14:0*	*16:0*	*16:1*	*18:0*	*18:1*	*18:2*	*18:3*
Vegetable oils										
Coconut oil*	20–23	8–10	47.4	18.0	8.0	–	2.8	5.6	1.6	–
Corn oil	18–20	115–127	–	–	12.0	–	2.7	30.1	54.7	1.4
Olive oil	17–26	79–90	–	–	14.0	1.3	2.6	74.0	8.1	–
Safflower oil	16	145	–	0.2	12.3	–	1.8	11.2	74.3	0.2
Soybean oil	20–21	130–138	–	–	11.5	–	4.3	27.3	49.7	6.9
Animal fats										
Beef tallow	38–43	35–45	–	3.3	26.2	–	22.4	45.3	1.6	0.5
Lard	36–43	50–65	–	1.5	25.7	–	12.1	49.2	9.6	1.1
Menhaden oil*	31–33	148–172	–	11.9	23.2	16.4	5.6	15.3	2.7	1.9
Poultry fat	–	80	0.2	1.4	21.4	6.8	5.9	39.5	23.5	1.0

*In addition to the fatty acids shown, coconut oil also contains 8:0—8.8%; 10:0—7.2%; menhaden oil also contains 14:1—0.4%; 16:4—2.4%; 20:4—2.0%; 20:5—11.3%; 22:5—0.7%; 22:6—7.6%.

theory of Verzar and the particulate theory of Frazer. The present concept has developed as a result of several independent research observations. Briefly these include the discoveries (1) that the upper intestinal mucosal cells contain microvilli; (2) that pancreatic lipase acts specifically upon the primary ester groups (positions 1- and 3-) of triglycerides; (3) that monoglycerides are absorbed intact, and (4) that lipid

Table 2.2. PROPERTIES OF THE COMMON FATTY ACIDS FOUND IN FEED FATS AND OILS

Fatty acid			*Molecular weight*	*Iodine value*	*Melting point °C*
Common name	*Systematic name*	*Designation*			
Lauric	Dodecanoic	12:0*	200	0	43.6
Myristic	Tetradecanoic	14:0	228	0	53.8
Palmitic	Hexadecanoic	16:0	256	0	62.9
Stearic	Octadecanoic	18:0	285	0	69.9
Palmitoleic	9-Hexadecenoic	16:1	254	99.8	1.5
Oleic	9-Octadecenoic (cis)	18:1	283	89.9	14.0
Linoleic	9,12-Octadecadienoic (cis,cis)	18:2	281	181.0	− 5.0
Linolenic	9,12.15-Octadecatrienoic (cis,cis.cis)	18:3	279	273.5	−14.4
Arachidonic	5,8,11,14-Eicosatetraenoic (cis,cis,cis,cis)	20:4	305	316.2	−49.5
Timnodonic	4,8,12,15,18-Eicosapentaenoic (presumably all-cis)	20:5	302	335.7	—
Clupanodonic	4,8.12,15.19-Docosapentaenoic (presumably all-cis)	22:5	331	384.5	−78.0

*First number shows number of carbon atoms; number to right of colon shows number of double bonds.

solubilization in the lumen of the upper intestine results from the physico-chemical formation of a lipid-bile salt micelle. In addition, it has been shown that enzymatic reesterification pathways exist within the mucosal cells and that chylomicron formation is an important part of the total process of fat transport.

Investigations with the electron microscope have demonstrated that the surface of the upper intestinal mucosal cell, which originally was thought to be composed of tiny pores or canals, actually contains hundreds of small protoplasmic processes, termed microvilli. These are continuous with the intestinal epithelial cell and greatly increase the absorptive surface of each mucosal cell. Discovery of the existence of microvilli forced a search for a new mechanism to explain the absorption of large droplets from the lumen, a process of fat absorption which had been proposed by Frazer. Matson and associates discovered that pancreatic lipase shows specificity for the fatty acids esterified to glycerol in the 1- and 3- positions. This specificity of lipase leads first to 1,2-diglycerides, then to 2-monoglycerides. The 2-monoglycerides cannot be hydrolyzed as such, but may be broken down only if they are isomerized to 1-monoglycerides. The specificity of pancreatic lipase for the primary ester linkages of glycerides is not altered by the degree of unsaturation or chain length of the fatty acids involved.

Using isotopically-labeled monoglycerides, it has been shown that unhydrolyzed monoglycerides are absorbed intact. Fifty to seventy-eight per cent of the dietary triglyceride molecules are hydrolyzed to 2-monoglycerides and absorbed in this form.

In 1962, Hofmann and Borgstrom proposed that the formation of a lipid-bile salt micelle is an important physicochemical prerequisite for maximum fat absorption. Conjugated bile salts possess dissymmetric polar and non-polar regions; they are capable of reducing surface tension of aqueous solutions and behave as detergents. Certain water-insoluble compounds such as monoglycerides and unsaturated fatty acids cannot form micelles alone, but they readily form stable mixed micelles with the conjugated bile salts. These mixed micelles have the ability to solubilize significant amounts of the nonpolar fatty acids and the fat soluble vitamins. Compounds in the micelles are oriented with their polar groups extending out to the micellar surface. In contrast to large oil-water emulsion droplets, micelles form spontaneously and are only 30–100 Å in diameter. A solution of micelles is optically clear and very stable.

The lipid-bile salt micelle is able to dissolve relatively large amounts of nonpolar compounds within its liquid nonpolar interior. Thus, palmitic acid and stearic acid, which are water-insoluble, nonpolar fatty acids with high melting points, are only slightly soluble in bile

salts in emulsion form but are markedly solubilized in the presence of a mixed micelle. In this form the fatty acids and other lipid-like materials are solubilized in the aqueous phase of the lumen and are transported to the mucosal cell membrane.

Biochemical studies of the enzymatic processes within cells have demonstrated the existence of two reesterification pathways in the intestinal mucosal cell. One requires monoglycerides as the initial acceptor, the other, glycerol. The chylomicrons formed within the cells contain a central core of reesterified triglycerides surrounded by a membrane-like structure composed of protein, cholesterol and phospholipids. It is in this form that the reesterified triglycerides are transported from the intestinal mucosal cells to the systemic circulation of the body.

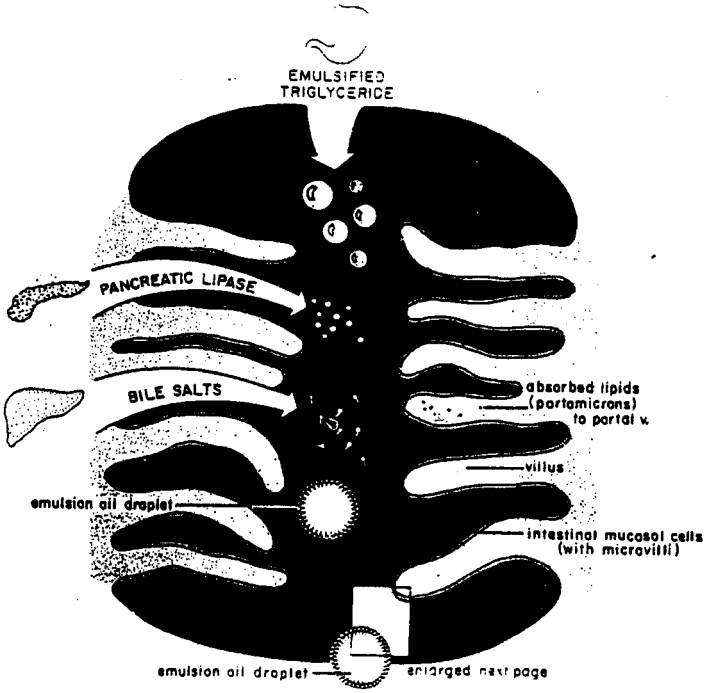


Fig. 2.9. Intraluminal section of the duodenum showing the initial stages of fat digestion.

The current theory of fat absorption may be summarized as shown in Figs. 2.9 and 2.10. Dietary lipids composed primarily of triglycerides enter the duodenum and become emulsified upon contact with the con-

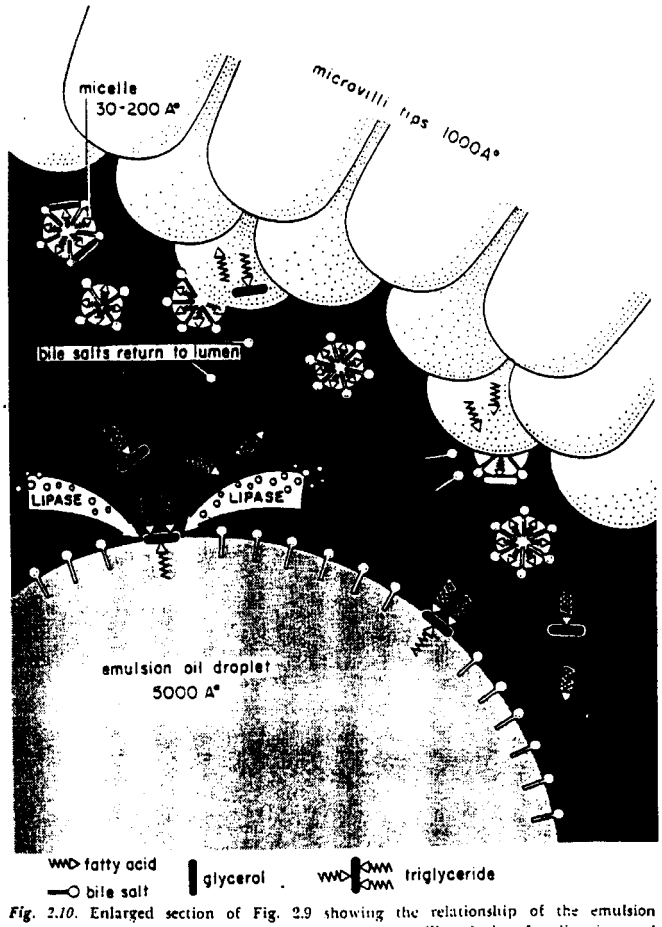
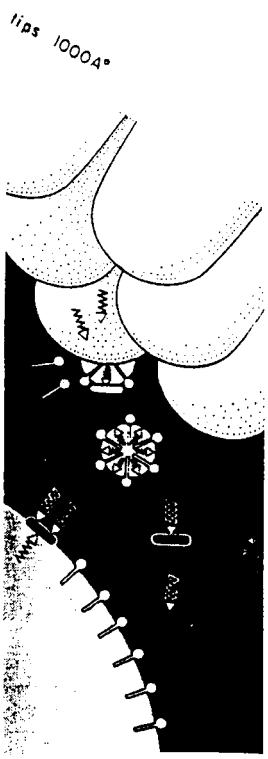


Fig. 2.10. Enlarged section of Fig. 2.9 showing the relationship of the emulsion droplet, lipase, micelles, and the tips of the microvillus during fat digestion and absorption.

y be summarized as shown in
ed primarily of triglycerides
i upon contact with the con-



he relationship of the emulsion
rovillus during fat digestion and

jugated bile salts. At the surface of these fairly large emulsion droplets (5000Å) the activity of pancreatic lipase is greatly accelerated. The fatty acids in the 1- and 3- positions of the triglycerides project into the aqueous phase of the intestinal contents and are readily acted upon by the pancreatic lipase. A portion of the released monoglycerides and the unsaturated fatty acids aid in the formation and stabilization of smaller emulsion droplets while most of the monoglycerides and unsaturated fatty acids, together with the conjugated bile salts, spontaneously form mixed micelles. These tiny particles, only 30 to 100 Å in diameter, become highly dispersed in the aqueous medium of the intestinal lumen. They solubilize the nonpolar fatty acids such as palmitic and stearic acids. In this form the fatty acids and the monoglycerides are readily brought into contact with the microvilli. Each intestinal epithelial cell contains approximately 1000 microvilli which increase the surface area of the intestinal epithelial membrane by 15 to 25 fold. Monoglycerides and fatty acids pass across this membrane into the mucosal cells. Since bile salts are not absorbed in the upper small intestine, they are continuously re-utilized for subsequent micelle formation and are eventually absorbed in the lower jejunum.

The percentage absorbability of fats or fatty acids is influenced by the following factors: (1) The chain length of the fatty acids; (2) the number of double bonds in the fatty acid; (3) the presence or absence of ester linkages, or whether the fat is in the form of triglyceride or as a free fatty acid; (4) the specific arrangement of the saturated and unsaturated fatty acids on the glycerol moiety of a triglyceride molecule; (5) age of the chicken; (6) the ratio of unsaturated to saturated fatty acids in the mixture of free fatty acids; (7) the intestinal microflora; (8) the composition of the diet in which the fatty acids are fed; and (9) the amount and types of triglycerides in the dietary fat mixture.

It appears that oleic and linoleic acids, and various monoglycerides, readily form mixed micelles with bile salts and these mixed micelles solubilize the saturated fatty acids. This effect is shown in Fig. 2.11 by the improvement in absorption of palmitic when fed with increasing amounts of oleic acid or monoolein.

It is also apparent that monoolein is more effective than oleic acid in the improvement of absorption of palmitic acid. This appears to be due to the fact that monoolein forms a mixed micelle which will solubilize larger amounts of palmitic acid. Thus, in a feeding situation whereby the major portion of the fat in a feed happened to be of the *saturated* type, improvement in absorbability and therefore in energy value would result from addition to the feed of a small amount of vegetable oil containing a preponderance of unsaturated fatty acids.

Appendix 10

EXHIBIT C

NUTRITION AND MANAGEMENT of DUCKS

By

MILTON L. SCOTT, Ph.D.
Jacob Gould Schurman Professor of Nutrition, Emeritus

and

WILLIAM F. DEAN, Ph.D.
Director, Duck Research Laboratory

Cornell University *Ithaca, New York*

1991

PUBLISHED BY
M. L. SCOTT OF ITHACA
P.O. Box 4464, Ithaca, NY 14852

mixed with water in large dough mixers and the wet mash transported in small cars on tracks to the duck pens where it was shoveled into troughs by hand (Wilcox, 1949). Wetting the mash overcame the problem of the feed caking on mouthparts and made possible a much greater rate of feed consumption. However this method of feeding was very labor intensive and feed mixed too far in advance or feed left in troughs often became moldy. Pelleted feeds solved the problems associated with both dry and wet mash feeding. Numerous studies have demonstrated marked improvements in weight gain and feed conversion when pellets are fed in place of mash (Heuser and Scott, 1951; Wilson, 1973, Dean, 1986). Pelleted feeds are commonly accepted today as the standard for intensive duck production. In the course of establishing nutrient requirements of ducks it has become apparent that in order to obtain the most meaningful results, nutrition experiment should be carried out with pelleted diets.

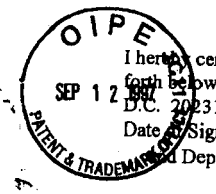
One problem that is sometimes associated with the use of pelleted duck feeds is the accumulation of fines in the feeding equipment. During the manufacturing and handling of pelleted feeds some fines are unavoidably produced. Duck farmers may rank pellet quality high on their list of criteria for selecting a feed supplier. In an effort to quantify the effect of different levels of fines in feeds on performance, Dean (1986) fed ducklings diets that were identical, except for containing 0, 2, 4, 8 and 16% fines. All of these diets resulted in similar body weights at 42 days of age. However, the amount of feed required per unit of body weight was increased by 2.0% and 2.8% when the diet contained 8% and 16% fines, respectively. The adverse effects of these two highest levels of fines, while significant and important, were not as detrimental to performance as the appearance of such diets might suggest.

Ducks prefer pellets to mash when given a choice. When fines are allowed to accumulate they limit feed intake and interfere with the normal flow of pellets into the feed hopper. This problem can be prevented by withholding pellets periodically, thus forcing the ducks to clean up the accumulated fines. Feed manufacturers sometimes encounter difficulty in pelleting certain types of diets. Optimizing pelleting conditions (die thickness, particle size, temperature, moisture, cooling etc.) may solve this problem. However, pellet binders are often used as an aid in maintaining satisfactory pellet durability. Studies were conducted at the Long Island duck laboratory by the junior author during the 1980's to determine relative value of some commercially available pellet binders in terms of pellet durability and performance of ducks. The results of these studies, presented in Table 2.2, demonstrated (1) that lignin sulfonate and hemicellulose extract binders significantly improved pellet durability; (2) that the effectiveness of lignin sulfonate increased with increasing dietary levels, up to 2.50% (the highest level fed); (3) that sodium bentonite, cellulose gum and a modified starch binder were ineffective as binding agents under the conditions of these ex-

G1816

PATENT

#8
9/23
10/6/97



I hereby certify that this correspondence is being deposited with the United States Postal Service on the date set forth below as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231

Date of Signature
Deposit: September 8, 1997

Thad F. Kryshak, Reg. No. 19,428

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Mark E. Cook et al
Serial No.:	08/684,785
Filed:	July 22, 1996
For:	METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN
Group Art No.:	1816
Examiner:	F. Pierre VanderVegt

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 CFR 1.97(c)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The enclosed documents were cited in a search conducted by the European Patent Office in a counterpart patent application to the one identified above. The documents are being submitted in compliance with 37 CFR 1.97 and 1.98. A list of documents on form PTO-1449 and a translation or a concise explanation of each non-English language document is enclosed herewith.

Certification

Each item of information contained in this Statement was cited in a communication from a foreign patent office in a counterpart foreign application. That citation was not more than three months prior to the filing of this Statement.

In view of the above certification a fee is not required for consideration of these documents. However, should a fee be deemed to be due by the Commissioner, such fee should be charged to Deposit Account No. 17-0055.

Respectfully submitted,

Dated: September 8, 1997 By: Thad F. Kryshak

Registration No. 19,428

Quarles and Brady
411 East Wisconsin Ave.
Milwaukee, WI 53202
(414) 277-5000

Form PTO-1449
(Rev. 2-88)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ATTY. DOCKET	APPLICATION NO.
960296.41	08/684,785

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use several sheets if necessary)

APPLICANT	
Mark E. Cook et al.	
FILING DATE	GROUP
7/22/96	1816

OIPE JC14 SEP 12 1997 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAMINER'S INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
R		0241441A1	10/14/87	EPO	~~C12~~	~~1/04~~	x	
		WO9421284	09/29/94	PCT	~~A61~~	37/54	x	
		0426463A2	05/08/91	EPO	~~A61~~	~~9/16~~	x	
		WO9101803	02/21/91	PCT	~~B01~~	13/04	x	
		0231817A2	08/12/87	EPO	~~A23~~	~~1/00~~		x

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER [signature] DATE CONSIDERED 11/10/97

* EXAMINER: Initial if a citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

QB1\295505.

Form PTO-1449
(Rev. 2-88)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ATTY. DOCKET No.	APPLICATION NO.
960296.9[illegible]511	08/684,785

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use several sheets if necessary)

APPLICANT	
Mark E. Cook et al.	
FILING DATE: 7/22/96	GROUP: 1816

U.S. PATENT DOCUMENTS

EXAMINER'S INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
RV		0707798A1	04/24/96	PCT	~~A23~~	~~1/00~~		x
		0556883A1	08/25/93	PCT	~~A23~~	~~1/16~~	x	
		WO9604933	02/22/96	PCT	~~A61~~	~~39/395~~	x	
		WO9622028	07/25/96	PCT	~~A23~~	~~1/00~~	x	

OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*

EXAMINER [signature] DATE CONSIDERED 11/10/97

* EXAMINER: Initial if a citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

QB1\295505.

PATENT

I hereby certify that this correspondence is being deposited with the United States Postal Services on the date set forth below as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington DC 20231.

Date of Signature and Deposit: Oct 29, 1997

Attorney of Record

9/B
S.G.S.
11/6/97
(NE)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Mark E. Cook et al.
Serial No.:	08/684,785
Filed:	July 22, 1996
For:	METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN
Group Art Unit:	1816
Examiner:	F. Pierre VanderVegt

OK TO ENTER
A/ 11/10/97

AMENDMENT AFTER FINAL REJECTION

Assistant Commissioner for Patents
Washington DC 20231

Dear Sir:

In response to the Office Action of October 6, 1997, please amend the claims as follows:

IN THE CLAIMS:

Cancel claims 6 to 10.

Add the following new claim:

B1

11. A particulate animal feed comprising an inner core of nutrients containing carbohydrates and proteins and an outer layer of an edible fat having cholecystokinin (CCK) antibodies encapsulated therein.

REMARKS

In view of the foregoing, it is believed that the application is now in allowable form and that a Notice of Allowance should be forthcoming.

Respectfully submitted,

MARK E. COOK
DARIA L. JEROME

By: Thad F. Kryshak

Thad F. Kryshak
Reg. No. 19,428
Quarles & Brady
411 East Wisconsin Avenue
Milwaukee, WI 532-24497
414-277-5781

10

AF/1816

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Mark E. Cook, et al.
Serial No.: 08/684,785
Filed: July 22, 1996
Title: METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN
Art Unit: 1816
Examiner: F. Pierre VanderVegt

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified patent application.
The fee for that amendment has been calculated as shown below:

CLAIMS AS AMENDED

	Claims After Amendment		Highest Number Paid For Previously	Number Extra	Rate	Additional Fee
Total Claims	1	Minus	20	0 X	$ 22.00	= $.00
Independent Claims	1	Minus	3	0 X	$ 82.00	= $.00
First presentation of a Multiple Dependent Claim					$270.00	= $.00
					Total Fee	$.00

[X] No additional fee is required.

[ ] A check for $ .00 to cover the filing fee and the cost of recording the assignment is enclosed.

[X] Please charge our Deposit Account No. 17-0055 in the amount of $.00. The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Account No. 17-0055. Two extra copies of this sheet are enclosed.

Respectfully submitted,

Dated: October 29, 1997

By: _____
Thad F. Kryshak
Registration No. 19,428

Quarles and Brady
411 East Wisconsin Ave.
Milwaukee, WI 53202
(414) 277-5781

QBMKE\4079285.1

Notice of Allowability

Application No.	Applicant(s)
08/684,785	Cook et al
Examiner: F. Pierre VanderVegt	Group Art Unit: 1816

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to *the Amendment After Final filed November 3, 1997*.

☒ The allowed claim(s) is/~~are~~ *11*.

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☐ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal lettter addressed to the Official Draftsperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☐ Interview Summary, PTO-413

☐ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☒ Examiner's Statement of Reasons for Allowance

REASONS FOR ALLOWANCE

Claims 6-10 have been canceled. New claim 11 has been added.

Claim 11 is currently pending in this application.

1. The following is an Examiner's statement of reasons for allowance:

Applicant's Amendment After Final Rejection filed November 3, 1997 has successfully addressed all remaining grounds of objection and rejection. In light of this amendment, all remaining rejections and objections are hereby withdrawn. The prior art of record does not teach or suggest the claimed invention.

Any comments considered necessary by Applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

2. Papers related to this application may be submitted to group 1800 by facsimile transmission. Papers should be faxed to group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1816 is (703)305-3014. *Communications which are not to be entered into the record, such as proposed amendments, should be clearly marked "DRAFT" and faxed to (703)305-7939.*

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Monday through Friday from 8:00 am to 4:30 pm ET. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the group 1800 receptionist, whose telephone number is (703)308-0196.

November 10, 1997
F. Pierre VanderVegt, Ph.D.
Patent Examiner
Art Unit 1816
d8

David A. Saunders
DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1816

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: Box ISSUE FEE
ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

18M1/1112

THAD F KRYSHAK
QUARLES & BRADY
411 EAST WISCONSIN AVE
MILWAUKEE WI 53202-4497

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
08/684,785	07/22/96	001	VANDERVEGT, F	1816	11/12/97

First Named Applicant: COOK, MARK E.

TITLE OF INVENTION: METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 960296.94011	424-442.000	U07	UTILITY	NO	$1320.00	02/12/98

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
If the SMALL ENTITY is shown as yes, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown and notify the Patent and Trademark Office of the change in status, or
B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statementof Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "6b" of Part B should be completed.

III. All communications regarding this application must give application number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTO UTILITY GRANT

Paper Number 11

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America for the term set forth below, subject to the payment of maintenance fees as provided by law.

If this application was filed prior to June 8, 1995, the term of this patent is the longer of seventeen years from the date of grant of this patent or twenty years from the earliest effective U.S. filing date of the application, subject to any statutory extension.

If this application was filed on or after June 8, 1995, the term of this patent is twenty years from the U.S. filing date, subject to an statutory extension. If the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121 or 365(c), the term of the patent is twenty years from the date on which the earliest application was filed, subject to any statutory extension.

Bruce Lehman
Commissioner of Patents and Trademarks

Attest Mary K Queen

The United States of America

PATENT AND TRADEMARK OFFICE
UNITED STATES OF AMERICA

Form PTO-1584 (Rev. 2/97)

(RIGHT INSIDE)

PART B—ISSUE FEE TRANSMITTAL

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 2 through 6 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advance orders and notification of maintenance fees will be mailed to addresses entered in Block 1 unless you direct otherwise, by: (a) specifying a new correspondence address in Block 3 below; or (b) providing the PTO with a separate "FEE ADDRESS" for maintenance fee notifications with the payment of Issue Fee or thereafter. See reverse for Certificate of Mailing, below.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, D.C. 20231.

DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Issue Fee, Assistant Commissioner for Patents, Washington D.C. 20231

DEC 4 1997

1. CORRESPONDENCE ADDRESS

THAD F KRYSHAK
QUARLES & BRADY
411 EAST WISCONSIN AVE
MILWAUKEE WI 53202-4497

18M1/1112

DEC 4 1997

2. INVENTOR(S) ADDRESS CHANGE (Complete only if there is a change)

INVENTOR'S NAME

Street Address

City, State and Zip Code

CO-INVENTOR'S NAME

Street Address

City, State and Zip Code

☐ Check if additional changes are enclosed

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/684,785	07/22/96	001	VANDERVEGT, F 1816	11/12/97

First Named Applicant: COOK, MARK E.

TITLE OF INVENTION: METHOD OF IMPROVING THE GROWTH OR THE EFFICIENCY OF FEED CONVERSION OF AN ANIMAL AND COMPOSITIONS FOR USE THEREIN

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 960296.94011	424-442.000	U07	UTILITY	NO	$1320.00	02/12/98

3. Correspondence address change (Complete only if there is a change)

12/03/1997 RJENNING 00000055 08684785
01 FC:142 1200.00 CH
02 FC:561 30.00 CH

4. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.

1 Quarles & Brady
2
3

5. ASSIGNMENT DATA TO BE PRINTED ON THE PATENT (print or type)

(1) NAME OF ASSIGNEE: Wisconsin Alumni Research Foundation

(2) ADDRESS: (CITY & STATE OR COUNTRY) Madison, Wisconsin

A. ☐ This application is NOT assigned.

X ☐ Assignment previously submitted to the Patent and Trademark Office.

☐ Assignment is being submitted under separate cover. Assignment should be directed to Box ASSIGNMENTS.

PLEASE NOTE: Unless an assignee is identified in Block 5, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

6a. The following fees are enclosed:
☐ Issue Fee ☐ Advance Order - # of Copies

6b. The following fees should be charged to:
DEPOSIT ACCOUNT NUMBER 17-0055
(ENCLOSE A COPY OF THIS FORM)
☒ Issue Fee ☒ Advance Order - # of Copies 10
☒ Any Deficiencies in Enclosed Fees

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

(Authorized Signature) (Date) 12/2/97

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

Certificate of Mailing

Note: If this certificate of mailing is used, it can be used to transmit the Issue Fee. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: **Box ISSUE FEE**
Assistant Commissioner for Patents
Washington, D.C. 20231

on: December 2, 1997 (Date)

Thad F. Kryshak (Name of person making deposit)

December 2, 1997 (Signature)

(Date)

EXPRESS MAIL LABEL NO. _____

PTO/SB/17 (6-95)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

002/PTO
Rev. 10/96

U.S. Department of Commerce
Patent and Trademark Office

FEE TRANSMITTAL

TOTAL AMOUNT OF PAYMENT	$ 1320.00

Complete If Known	
Application Number	08/684,785
Filing Date	7/22/97
First Named Inventor	Mark E. Cook
Group Art Unit	1816
Examiner Name	F. Vandervegt
Attorney Docket Number	960296.94011

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 17-0055

Deposit Account Name: Quarles & Brady

[X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17 [ ] Charge the Issue Fee Set in 37 CFR 1.18 at the Mailing of the Notice of Allowance, 37 CFR 1.311(b)

2. [ ] Payment Enclosed:

[ ] Check [ ] Money Order [ ] Other

FEE CALCULATION (fees effective 10/01/97)

1. FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	790	201	395	Utility filing fee	
106	330	206	165	Design filing fee	
107	540	207	270	Plant filing fee	
108	790	208	395	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($)

2. CLAIMS

		Extra		Fee from below		Fee Paid
Total Claims		-20=		X	=	
Independent Claims		-3=		X	=	
Multiple Dependent Claims					=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	82	202	41	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim
109	80	209	40	Reissue independent claims over original patent
110	22	210	11	Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)		Fee
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	*920	112	*920	Requesting publication of SIR prior to Examiner action	
113	*1,840	113	*1,840	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for response within first month	
116	400	216	200	Extension for response within second month	
117	950	217	475	Extension for response within third month	
118	1,510	218	755	Extension for response within fourth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive unavoidably abandoned application	
141	1,320	241	660	Petition to revive unintentionally abandoned application	
142	1,320	242	660	Utility issue fee (or reissue)	1320
143	450	243	225	Design issue fee	
144	670	244	335	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	790	246	395	Filing a submission after final rejection (37 CFR 1.129(a))	
149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____

Other fee (specify) _____

SUBTOTAL (3) ($) 1320

* Reduced by Basic Filing Fee Paid

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	Thad F. Kryshak			Reg. Number	19,428
Signature	Thad F. Kryshak	Date	12/2/97	Deposit Account User ID	

Burden Hour Statement: This form is estimated to take .2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. 4095236

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1995

Application or Docket Number: 08/684785

CLAIMS AS FILED - PART I

	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA
FOR		
BASIC FEE		
TOTAL CLAIMS	8 minus 20 =	*
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY RATE	SMALL ENTITY FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
	375.00	OR		750.00
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL		OR	TOTAL	750

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	
x39=		OR	x78=	
+125=		OR	+250=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Form ...30
(REV ...)

PACE DATA ENTRY CODING SHEET

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

1ST EXAMINER Holloway	DATE 9-5-96
2ND EXAMINER	DATE

APPLICATION NUMBER	TYPE APPL	FILING DATE MONTH	DAY	YEAR	SPECIAL HANDLING	GROUP ART UNIT	CLASS	SHEETS OF DRAWING
08/684785	1	07	29	96	0	1816	424	

TOTAL CLAIMS	INDEPENDENT CLAIMS	SMALL ENTITY?	FILING FEE	FOREIGN LICENSE	ATTORNEY DOCKET NUMBER
18	2	0	750	Y	960296.9401 1

CONTINUITY DATA

CONT CODE	STATUS CODE	PARENT APPLICATION SERIAL NUMBER	PCT APPLICATION SERIAL NUMBER	PARENT PATENT NUMBER	PARENT FILING DATE MONTH	DAY	YEAR
			PCT/				
			PCT/				
			PCT/				
			PCT/				
			PCT/				

PCT/FOREIGN APPLICATION DATA

FOREIGN PRIORITY CLAIMED	COUNTRY CODE	PCT/FOREIGN APPLICATION SERIAL NUMBER	FOREIGN FILING DATE MONTH	DAY	YEAR

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(12), 2035-2039 (1994)

IMPROVED STABILITY OF LIPID COATED VITAMIN A IN ANIMAL FEED ADDITIVES

R.B.Albright (1) AND C.H.Kowarski (2) *

(1)Lambert-Kay div. of Carter-Wallace , Cranbury N.J.
(2)Temple University School of Pharmacy, Phila. Pa.

ABSTRACT

Lipids have been studied as methods of encapsulation, permeation enhancers, and as drug delivery systems. A lipid coating containing lecithin,cholesterol and functionalized stearyls was utilized in this study to inhibit the mineral catalyzed Vitamin A degradation in a dry flowable animal feed additive. Results indicate much improved stability.

INTRODUCTION

Vitamin A is very susceptable to oxidation, heat, light, moisture and metal catalysis. (1) (2). Oxidation and hydrolysis are accelerated at high temperatures. Solid formulations are as unstable as liquid Vitamin A products due to the large surface area present for reaction (3). In feed mixtures, the presence of water, peroxides, minerals and peroxidized unsaturated fats all add to the instability of Vitamin A.

Mineral mixtures ordinarily are used to supply calcium, phosphorus and trace minerals to animals and can catalyze the oxidative degradation of Vitamin A.

Vitamin A undergoes both pseudo-zero and first order reactions in liquid media (2). Carstensen has found a log-linear ratio between the first order rate constant and water-vapor pressure (5). Controlling the humidity is one method of improving Vitamin A stability in the solid matrix. Vitamin A solid preparations have shown increased stability when Vitamin A was encapsulated in gelatin (2).

The purpose of this study is to investigate the use of lipid coatings on a powder containing absorbed Vitamin A. The formulation is specifically a vitamin/mineral feed supplement for use in animal nutrition.

By coating a vitamin A dispersion in the components of a lipid bilayer, two results may be realized:

1. Stability from mineral catalyzed degradation.
   The lipid bilayer may halt the catalytic decomposition reaction by physically separating Vitamin A fron the mineral components.

* To whom inquiries should be addressed

2. Stability from hydrolytic degradation. If water permeates the bilayer it may be encapsulated by so-called liposome formation and not be available to interact with vitamin A.

MATERIALS AND METHODS

The following materials were used in this study: Vitamin A Palmitate 1,000,000 I.U./ gram was a gift of Hoffman-LaRoche. Lecithin (dry) was food grade and purchased from Central Soya (Decatur, Ill.). Stearylamine was purchased from Aldrich Chemical and Cholesterol U.S.P. , Stearic Acid N.F. and Stearyl Alcohol N.F. were purchased from Ruger Chemical. The Lambert-Kay division of Carter-Wallace gave the vitamin/mineral premix used in this study.

The vitamin/mineral premix used in the study is a nutritionally complete mixture of vitamins, amino acids and the following minerals: calcium,phosphorus, potassium, sodium, magnesium, iron, copper, zinc, manganese, and cobalt, as pharmaceutically acceptable salts.

Formulations were prepared in a 5 Kg. Hobart blender at ambient temperature. The Vitamin A Palmitate was adsorbed onto a dry carrier such as Potassium Phosphate Monobasic (Anhydrous). The lipid composition was then melted in a seperate vessel (neat) and poured onto the agitating Vitamin A coated carrier. After agitation and cooling (30 minutes), the vitamin/mineral premix was added. Agitation continued for 15 minutes . Total mixing time was 45 minutes. The lab prep was done at ambient temperature and relative humidity. No requirements for an inert atmosphere were utilized.

ANALYTICAL METHOD

Vitamin A stability of the powder was analyzed by HPLC using a 0.4 X 30 cm. Porasil column at 313 nm. using a mobile phase of 98:2 Isooctane : Ethyl Ether . Stock and working solutions of Vitamin A palmitiate were prepared in hexane and a calibration curve was prepared. Sample preparation consisted of weighing 50-60 mg of sample into 5 ml DMSO. Extraction of the Vitamin A was done with heat and agitation. 25 ml of hexane was added and agitation and centrfugation followed. 5 mls of the supernatent was pipetted into a 50 ml volumetric flask and was diluted with hexane. The injection volume was 7 microliters.

STABILITY TESTING

Formulations 1 through 4 were analyzed in accordance with the preceeding HPLC method. Storage stability samples of the formulations were analyzed initially, at 1 month, 3 months and 6 months. The samples were stored in the following conditions: ambient temperature (approx.25 degrees), and 37 degrees centigrade in dark cabinets or ovens. Analyses were run in duplicate and averaged for data analysis.

The finished formulae were split into 300 gram amber tinted polystyrene wide mouth bottles, filled to the top and sealed with a torque of 10 to 20 foot-pounds and stored at the indicated conditions. Intial analysis was done to verify initial concentration and recovery. Each bottle was considered a sample volume and duplicate weighings were done for analysis.

Samples were analyzed by HPLC as previously indicated. The results were averaged and normalized to percent of initial assay (100%) (Table 2). All samples were analyzed for moisture content by Karl Fischer method. In all samples, moisture content was below 1 %.

DISCUSSION OF RESULTS

Table 3 is a comparision of zero order and (pseudo) first order constants and their R-squared values. These results were developed from the stability data of Table 2. Once the

TABLE 1
Formulations of Lipid Coated Powders

FORMULATIONS NUMBER:	1.	2.	3.	4.
LECITHIN	-	1.69	1.69	1.69
CHOLESTEROL	-	0.83	0.83	0.83
STEARIC ACID	-	-	0.28	-
STEARYLAMINE	-	0.28	-	-
STEARYL ALCOHOL	-	-	-	0.28
VITAMIN A PALMITATE	0.61	0.61	0.61	0.61
POTASSIUM PHOSPHATE MONOBASIC (ANH.)	57.68	54.98	54.98	54.98
VIT./MINERAL PREMIX	41.71	41.61	41.61	41.61

TABLE 2
Storage Stability Results
% OF Initial Vitamin A Concentration

FORMULA :	1 (CONTROL)		2		3		4	
TEMPERATURE :	R.T.	37	R.T.	37	RT	37	R.T.	37
1 MONTH	85.2	69.0	92.2	75.0	102	92.1	101.1	90.9
3 MONTHS	93.6	63.0	96.1	34.7	93.9	74.8	100.3	77.9
6 MONTHS	43.3	42.0	75.0	26.0	90.2	56.1	97.0	60.1

R.T. is room temperature
37 is 37 degrees centigrade

TABLE 3

Comparision Of Slopes and Regression Coefficients
Of Zero Order and Pseudo-First Order Degradation Profiles

FORMULATION	TEMP	ZERO ORDER		PSEUDO-FIRST ORDER	
		SLOPE	R	SLOPE	R
1 (CONTROL)	R.T.	-5.23	0.7	-10.81	0.61
	37	-11.13	0.69	-11.27	0.97
2	R.T.	-4.16	0.93	-7.51	0.58
	37	-22.12	0.99	-17.92	0.89
3	R.T	-1.95	0.88	-2.31	0.58
	37	-7.38	0.99	-9.81	0.82
4	R.T	-0.58	0.72	-0.50	0.25
	37	-6.60	0.99	-0.86	0.84

TABLE 4
Summary Of Lipid Formulae Reaction Kinetics

PRODUCT	TEMP	REACTION ORDER	%LOSS/DAY	VITAMIN A LOSS/DAY
1 (CONTROL)	R.T.	1	0.172	258
	37 DEGREES	1	0.366	549
2	R.T.	0	0.137	205.5
	37 DEGREES	0	0.727	1090.5
3	R.T.	0	0.064	96.0
	37 DEGREES	0	0.243	394.5
4	R.T.	0	0.019	28.5
	37 DEGREES	0	0.217	325.5

Vitamin A loss per day is based on a normalized initial dose of 150,000 I.U.

lipid coating is applied to the Vitamin A powder, it is interesting to note that the reaction order seems top shift from (pseudo) first order to zero order. This shift is most obvious in the 37 degree data. This may indicate that the decomposition pathway may have changed. This will be the subject of future investigation.

The evaluated temperature data in all cases indicates a substantial increase in degradation of 37 degrees over room temperature for each system. This is due to the low melting range of the lipid coating. In all cases the lipid coating begins its phase transition at 35 degrees. This must be taken into consideration for purposes of commercial utility.

The addition of the lipid coatings to a dispersion of Vitamin A powders definitely increases stability at room temperature (TABLE 4). The decomposition of Vitamin A is retarded in each experimental system as follows:

EXPERIMENT	SYSTEM	FACTOR OF STABILITY IMPROVEMENT
1	CONTROL	1
2	LECITHIN/CHOLESTEROL/ STEARYLAMINE	2.63
3	LECITHIN/CHOLESTEROL/ STEARIC ACID	5.55
4	LECITHIN/CHOLESTEROL/ STEARYL ALCOHOL	20.0

This data indicates that a lipid coating deposited on the substrate containing absorbed Vitamin A retards degradation of the vitamin while in the presence of minerals which would otherwise catalyze degradation.

REFERENCES

1.Harris, Robert , The Vitamins , 2nd Edition Volume 1 Academic Press NY 1967 p.245

2. Connors, K.A., Amidon, G.L., and Kennon, L.., Chemical Stability of Pharmaceuticals, John Wiley 1979 p.327

3.Buhler V. Vandemecum for Vitamin Formulations , Wissen Schafitiche, Verlagsgese II Shaft. mb H Stuttgart (1988)

4. Halverson A.W. and Hendrick C.M., Poultry Sci. 34:355 (1955)

5 Carstensen, J.T. J.Pharm. Sci. 53:839 (1964)

CURRICULUM VITAE

Name: Mark Eric Cook
15 Kewaunee Ct.
Madison, WI 53705

Office Address: University of Wisconsin
Animal Sciences Department
1675 Observatory Dr., Rm. 260
Madison WI 53706-1284

Phone: 608/262-7747

FAX: 608/262-5157

Current Title: Professor

Department: Poultry Science, University of Wisconsin-Madison

Education:

1982-1983 University of Wisconsin-Madison
Poultry Science Department
Postdoctorate

1980-1982 Louisiana State University
Department of Veterinary and Poultry Science
Ph.D. in Poultry Nutrition, minor in Immunology
Thesis: Leg Weakness: Interactions of avian reoviruses and nutrition in disease and immunological responses

1978-1980 Louisiana State University
Department of Poultry Science
M.S. in Poultry Nutrition
Thesis: The effects of dietary protein and calorie levels on the immune response of broiler chicks.

1974-1978 Louisiana State University
Department of Microbiology
B.S.

Professional Experience:

1996-current Director of the Poultry Research Institute
University of Wisconsin, Madison, WI

1994-1996 Director of Poultry Science Association

1992-current Professor
Department of Poultry Science
University of Wisconsin, Madison, WI

1990-1992	Associate Professor Department of Poultry Science University of Wisconsin, Madison, WI
1989-current	Associate Editor, Poultry Science
1989-1990	Visiting Professor Department of Poultry Science The Pennsylvania State University University Park, PA
1988-1989	Associate Professor Department of Poultry Science University of Wisconsin, Madison, WI
1983-1988	Assistant Professor Department of Poultry Science University of Wisconsin, Madison, WI
1982-1983	Postdoctorate and Lecturer Department of Poultry Science University of Wisconsin, Madison, WI
1980-1982	Research Assistant Department of Veterinary Science Louisiana State University, Baton Rouge, LA
1978-1980	Research Assistant Department of Poultry Science Louisiana State University, Baton Rouge, LA

Affiliate Appointments:

1986-current	Affiliate Faculty Environmental Toxicology Center University of Wisconsin, Madison, WI
1989-current	Affiliate Faculty Department of Nutritional Science University of Wisconsin, Madison, WI

1989-1995 Affiliate Faculty
NASA Center of Cell Biology
The Pennsylvania State University
University Park, PA

1994-current Affiliate Faculty
Department of Food Microbiology and Toxicology
University of Wisconsin, Madison, WI

Teaching Responsibilities:

Comparative Animal Nutrition. Typical enrollment: 60 students per year. A basic course in nutritional principles, metabolism and biochemistry. Cross-listed in Dairy Science, Meat and Animal Science, Nutritional Science, and Poultry Science.

Management for Avian Health. Typical enrollment: 20 students per year. Covers methods for the prevention and diagnosis of disease in poultry flocks.

Introduction to Poultry. Typical enrollment: 15 students per year. An applied course introducing poultry production, with a laboratory.

Immunotoxicology. Typical enrollment: 20 students every third year. Graduate course in current topics in environmental toxicology as related to the immune function of animals.

Seminar on the Integrated Poultry Industry. Typical enrollment: 10 students per year. Senior seminar.

Seminar in Environmental Toxicology. Typical enrollment: 40 students. Graduate seminar.

Graduate Students: Completed 7 M.S., 6 Ph.D.
Current 4 Ph.D.

Professional Organizations: Poultry Science Association
Sigma Xi
American Chemical Society
World's Poultry Science Association
Gamma Sigma Delta

Research Focus: Mode of action of nutrients, toxins, drugs, and chemicals in metabolism, metabolic disease, and immune responses of birds.

Honors: Purina Mills Award for Teaaching, 1990
ASCOP Fellow, 1994

Refereed Articles:

Cook, M.E., T.R. Scott, J.A. Hebert, and W.A. Johnson, 1982. Effects of blood sampling by cardiac puncture on subsequent body weights of boilers. Poultry Sci. 61:2506-2508.

Cook, M.E., and W.T. Springer, 1983. Effect of reovirus infection and dietary levels of selected vitamins on immunocompetence of chickens. Avian Dis. 27:367-377.

Cook, M.E., and M.L. Sunde, 1983. Performance of chicks fed diets composed of single ingredients or combinations of ingredients: A laboratory demonstration for undergraduates. World's Poultry Sci. J. 40:207-214.

Cook, M.E., P.H. Patterson, and M.L. Sunde, 1984. Leg deformities: Inability to increase severity by increasing body weight of chicks and poults. Poultry Sci. 63:620-627.

Cook, M.E., W.T. Springer, and J.A. Hebert, 1984. Enhanced incidence of leg abnormalities in reovirus WVU 2937 infected chickens fed various dietary levels of selected vitamins. Avian Dis. 28:548-561.

Cook, M.E., W.T. Springer, K.M. Kerr, and J.A. Hebert, 1984. Severity of tenosynovitis in reovirus-infected chickens fed various dietary levels of choline, folic acid, manganese, biotin, or niacin. Avian Dis. 28:526-573.

Cook, M.E., M.L. Sunde, J.L. Stahl, and L.E. Hanson, 1984. Zinc deficiency in pheasant chicks fed practical diets. Avian Dis. 28(4):1102-1109.

Ameenuddin, S., M.L. Sunde, and M.E. Cook, 1985. Essentiality of vitamin D_3 and its metabolites in poultry nutrition: A review. World's Poultry Sci. Assn. J. 41:52-63.

Dafwang, I.I., M.E. Cook, M.L. Sunde, and H.R. Bird, 1985. Bursal, intestinal, and spleen weights and antibody response of chicks fed subtherapeutic levels of dietary antibiotics. Poultry Sci. 64:634-639.

Ameenuddin, S., M.L. Sunde, H.F. DeLuca, and M.E. Cook, 1986. Excessive cholecalciferol in a layers diet: Decline in some aspects of reproductive performance and increased bone mineralisation of progeny. Brit. Poultry Sci. 27:671-677.

Crenshaw, T.D., M.E. Cook, J. Odle, and R.E. Martin, 1986. Effect of nutritional status, age at weaning, and room temperature on growth and systemic immune response of weanling pigs. J. Anim. Sci. 63:1845-1853.

Dafwang, I.I., M.E. Cook, D.J. Pringle, and M.L. Sunde, 1986. Nutritional value of aerobically fermented poultry manure and offal (Fermway) for broiler chicks. Poultry Sci. 65:1765-1770.

Patterson, P.H., M.E. Cook, T.D. Crenshaw, and M.L. Sunde, 1986. Mechanical properties of the tibiotarsus of broilers and poults loaded with artificial weight and fed various dietary protein levels. Poultry Sci. 65:1357-1364.

Stahl, J.L., M.E. Cook, and M.L. Sunde, 1986. Zinc supplementation: Its effect on egg production, feed conversion, fertility, and hatchability. Poultry Sci. 65:2104-2109.

Bates, D.P., L.E. Hanson, M.E. Cook, B.C. Wentworth, M.L. Sunde, and J.J. Bitgood, 1987. Lighting and sex ratio for breeding ringnecked pheasants in confined housing. Poultry Sci. 66:605-612.

Dafwang, I.I., M.E. Cook, and M.L. Sunde, 1987. Interaction of dietary antibiotic supplementation and stocking density on broiler chick performance and immune response. Brit. Poultry Sci. 28:47-55.

Gildersleeve, R.P., D.G. Satterlee, T.R. Scott, D.I. McRee, C.R. Parkhurst, M.E. Cook, 1987. Hematology of Japanese quail selected for high or low serum corticosterone responses to complex stressor. Comp. Biochem. Physiology: Physiology A 86A:569-573.

Greger, J.L., M.L. Storey, J.L. Stahl, M.E. Cook, S.E. Gentry-Roberts, and J.C. Lynds, 1987. Zinc, iron and copper interactions in humans, rats and chicks. Tr. Elem. Nutr. in Man and Animals 6:231-232.

Pimentel, J.L., and M.E. Cook, 1987. Suppressed humoral immunity in chicks fed diets deficient in sodium, chloride, or both sodium and chloride. Poultry Sci. 66:2005-2010.

Tsiagbe, V.K., M.E. Cook, A.E. Harper, and M.L. Sunde, 1987. Assessment of softness properties of feathers. Poultry Sci. 66:1600-1602.

Tsiagbe, V.K., M.E. Cook, A.E. Harper, and M.L. Sunde, 1987. Efficacy of cysteine in replacing methionine in the immune responses of broiler chicks. Poultry Sci. 66:1138-1146.

Tsiagbe, V.K., M.E. Cook, A.E. Harper, and M.L. Sunde, 1987. Enhanced immune responses in broiler chicks fed methionine-supplemented diets. Poultry Sci. 66:1147-1154.

Tsiagbe, V.K., R.J. Straub, M.E. Cook, A.E. Harper, and M.L. Sunde, 1987. Critical vitamin supplementation of broiler diets high in alfalfa juice protein. Poultry Sci. 66:1771-1778.

Tsiagbe, V.K., R.J. Straub, M.E. Cook, A.E. Harper, and M.L. Sunde, 1987. Formulating wet alfalfa juice protein concentrate diets for chicks. Poultry Sci. 66:1023-1027.

Chu, Q., M.E. Cook, W. Wu, and E.B. Smalley, 1988. Research Note: Immune and bone properties of chicks consuming corn contaminated with a *Fusarium* that induces dyschondroplasia. Avian Dis. 32:132-136.

Pimentel, J.L., and M.E. Cook, 1988. Improved growth in the progeny of hens immunized with jackbean urease. Poultry Sci. 67:434-439.

Ricke, S.C., D.M. Schaefer, M.E. Cook, and K.H. Kang, 1988. Differentiation of ruminal bacterial species by enzyme-linked immunosorbent assay using egg yolk antibodies from immunized chicken hens. Appl. Envir. Micro. 54:596-599.

Tsiagbe, V.K., M.E. Cook, A.E. Harper, and M.L. Sunde, 1988. Alterations in phospholipid composition of egg yolks from laying hens fed choline- and methionine-supplemented diets. Poultry Sci. 67:1717-1724.

Stahl, J.L., M.E. Cook, and J.L. Greger, 1989. Zinc, iron and copper content of eggs from hens fed varying levels of zinc. J. Food Composition 1:309-315.

Stahl, J.L., M.E. Cook, M.L. Sunde, and J.L. Greger, 1989. Enhanced humoral immunity in progeny chicks from hens fed practical diets supplemented with zinc. Appl. Agric. Res. 4:86-89.

Stahl, J.L., J.L. Greger, and M.E. Cook, 1989. Zinc, copper, and iron utilisation by chicks fed various concentrations of zinc. Brit. Poultry Sci. 30:123-134.

Burdsall, H.H., M. Banik, and M.E. Cook, 1990. Serological differentiation of three species of *Armillaria* and *Lentinula edodes* by enzyme-linked immunosorbent assay using immunized chickens as a source of antibodies. Mycologia 82:415-423.

Poernama, F., S.A. Schreyer, J.J. Bitgood, M.E. Cook, and A.D. Attie, 1990. Spontaneous high density lipoprotein deficiency syndrome associated with a Z-linked mutation in chickens. J. Lipid Res. 31:955-963.

Schrank, C.S., M.E. Cook, and W.R. Hansen, 1990. Immune response of mallard ducks treated with immunosuppressive agents: Antibody response to erythrocytes and *in vivo* response to phytohemagglutinin-P. J. Wildlife Dis. 26:307-315.

Stahl, J.L., J.L. Greger, and M.E. Cook, 1990. Breeding-hen and progeny performance when hens are fed excessive dietary zinc. Poultry Sci. 69:259-263.

Wu, W., M.E. Cook, and E.B. Smalley, 1990. Prevention of thiram-induced dyschondroplasia by copper. Nutr. Res. 10:555-557.

Wu, W., P.E. Nelson, M.E. Cook, and E.B. Smalley, 1990. Fusarochromanone production by *Fusarium* isolates. Appl. Envir. Micro. 56:2989-2993.

Cook, M.E., 1991. Nutrition and the immune response of the domestic fowl. CRC Poultry Biology 3:167-189.

Cook, M.E., 1991. Mycotoxin and nutrient interactions. 40th Western Dis. Conf., pp. 51-54.

Orth, M.W., D.A. Martinez, M.E. Cook, and A.C. Vailas, 1991. Non-reducible crosslink formation in tibial dyschondroplastic growth plate cartilage from broiler chicks fed homocysteine. Biochem. Biophys. Res. Comm. 179:1582-1586.

Payne, C., M.E. Cook, T.M. Ellis, and R.E. Hams, 1991. ELISA testing of U.S. breeders and layers for big liver and spleen disease (BLS). 40th Western Dis. Conf., pp. 216-218.

Pimentel, J.L., M.E. Cook, and J.L. Greger, 1991. Bioavailability of zinc-methionine for chicks. Poultry Sci. 70:1637-1639.

Pimentel, J.L., M.E. Cook, and J.L. Greger, 1991. Immune response of chicks fed various levels of zinc. Poultry Sci. 70:947-954.

Pimentel, J.L., M.E. Cook, and J.M. Jonsson, 1991. Research Note: Increased growth of chicks and poults obtained from hens injected with jackbean urease. Poultry Sci. 70:1842-1844.

Poernama, F., R. Subramanian, M. Cook, and A. Attie, 1991. High density lipoprotein deficiency syndrome in chickens is not associated with an increased susceptibility to atherosclerosis. Arteriosclerosis thrombosis 12:601-607.

Wu, W., M.E. Cook, and E.B. Smalley, 1991. Decreased immune response and increased incidence of tibial dyschondroplasia caused by *Fusaria* grown on sterile corn. Poultry Sci. 70:293-301.

Bai, Y., M.L. Sunde, and M.E. Cook, 1992. Wheat middlings as an alternate feedstuff for laying hens. Poultry Sci. 71:1007-1014.

Orth, M.W., Y. Bai, I.H. Zeytun, and M.E. Cook, 1992. Excess levels of cysteine and homocysteine induce tibial dyschondroplasia (TD) in broiler chicks. J. Nutr. 122:482-487.

Pimentel, J.L., M.E. Cook, and J.L. Greger, 1992. Anemia induced by ingestion of excess zinc in chicks: Importance of red blood cell turnover. J. Nutr. Biochem. 3:146-150.

Pimentel, J.L., J.L. Greger, M.E. Cook, and J.L. Stahl, 1992. Iron metabolism in chicks fed various levels of zinc and copper. J. Nutr. Biochem. 3:140-145.

Banik, M.T., J.A. Paul, H.H. Burdsall, and M.E. Cook, 1993. Serological differentiation of two forms of *Phellinus weirii*. Mycologia 85:605-611.

Cook, M.E., C.C. Miller, Y. Park, and M. Pariza, 1993. Immune modulation by altered nutrient metabolism. Nutritional control of immune-induced growth depression. Poultry Sci. 72:1301-1305.

Orth, M.W., D.A. Martinez, M.E. Cook, and A.C. Vailas, 1993. The presence of lysylpyridinoline in the hypertrophic cartilage of newly hatched chicks. Biochimica Biophys. Acta 1157:229-232.

Wu, W., M.E. Cook, Q. Chu, and E.B. Smalley, 1993. Tibial dyschondroplasia of chickens induced by fusarochromanone, a mycotoxin. Avian Dis. 37:302-309.

Bai, Y., and M.E. Cook, 1994. Histological study of tibial dyschondroplasia from light-type chicks fed cysteine-supplemented diets. Avian dis. 38:557-562.

Bai, Y., M.L. Sunde, and M.E. Cook, 1994. Egg production of laying hens before and after force-molting is not correlated. Appl. Poultry Res. 3:127-132.

Bai, Y. M.L. Sunde, and M.E. Cook, 1994. Molybdenum but not copper counteracts cysteine-induced tibial dyschondroplasia in broiler chicks. J. Nutr. 124:588-593.

Chin, S.F., J.M. Storkson, K.J. Albright, M.E. Cook, and M.W. Pariza, 1994. Conjugated linoleic acid is a growth factor for rats as shown by enhanced weight gain and improved feed efficiency. J. Nutr. 124:2344-2349.

Cook, M.E., Y. Bai, and M. Orth, 1994. Factors influencing growth plate cartilage turnover. Poultry Sci. 73:889-896.

Miller, C.C., and M.E. Cook, 1994. Evidence against the induction of immunological tolerance by feeding antigens to chickens. Poultry Sci. 73:106-112.

Miller, C.C., Y. Park, M.W. Pariza, and M.E. Cook, 1994. Feeding conjugated linoleic acid to animals partially overcomes catabolic responses due to endotoxin injection. Biochem. Biophys. Res. Comm. 198:1107-1112.

Orth, M.W., and M.E. Cook, 1994. Avian tibial dyschondroplasia: a description of the growth plate disease as well as the conditions that induce it. Vet. Pathol. 31:403-414.

Orth, M.W., R.M. Leach, A.C. Vailas, and M.E. Cook, 1994. Non-reducible collagen cross-linking in cartilage from broiler chickens with tibial dyschondroplasia. Avian Dis. 38:44-49.

Chu, Q., W. Wu, M.E. Cook, and E.B. Smalley, 1995. Induction of tibial dyschondroplasia and suppression of cell-mediated immunity in chickens by *Fusarium oxysporum* grown on sterile corn. Avian Dis. 39:100-107.

Hatch, K.A., K.A. Sacksteder, I.W. Treichel, M.E. Cook, and W.P. Porter, 1995. Early detection of catabolic state via change in $^{13}C/^{12}C$ ratio of blood protein. Biochem. Biophys. Res. Comm. 212:74[illegible]

Wages. D.P., M.D. Ficken, M.E. Cook, and J. Mitchell, 1995. Salt toxicosis in commercial turkeys. Avian Dis. 39:158-161.

Chu, Q., W. Wu, M.E. Cook, and E.B. Smalley, 1996. Elevated plasma glycosaminoglycans in chickens with tibial dyschondroplasia induced by a *Fusarium oxysporum* isolate. Avian Dis. 40:715-719.

Cook, M.E., 1996. Diet-induced immunosuppression. Pages 317-328 *in:* Poultry Immunology. T.F. Davison, T.R. Morris, and L.N. Payne, ed. Carfax Publishing Co., Oxfordshire, England.

Li, G., M.E. Cook, and W. Wu, 1996. Reduction of ferricyanide by thiamine or thiamine pyrophosphate. Biochem. Biophy. Res. Comm. 226:187-192.

Wu, W., M.E. Cook, F.S. Chu, T. Buttles, J. Hunger, and P. Sutherland, 1997. Case study of bovine dermatitis caused by oat straw infected with *Fusarium sporotrichioides*. Vet. Rec. 140:399-400.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
QUARLES & BRADY
Attn. Haas, George
411 East Wisconsin Avenue
Suite 2550
MILWAUKEE, WISCONSIN 53202-4497
UNITED STATES OF AMERICA

Applicant's or agent's file reference 960296.94011	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 97/01034	International filing date (day/month/year) 21/01/1997
Applicant WISCONSIN ALUMNI RESEARCH FOUNDATION	

Date of mailing (day/month/year) 14/07/1997

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Monika Schmitz

Form PCT/ISA/220 (January 1994)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
960296.94011		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 97/01034	21/01/1997	22/07/1996
Applicant		
WISCONSIN ALUMNI RESEARCH FOUNDATION		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/01034

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A23K1/00 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A23K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 241 441 A (MEDIPHARM AB) 14 October 1987 see page 3, line 21 - page 5, line 22 see claim 1 ---	1,6
Y	WO 94 21284 A (PHARMA PACIFIC PTY LTD ;CHANDLER DAVID SPENCER (AU); REED BENJAMIN) 29 September 1994 see page 9, line 6 - line 12 see examples 2,3 see claims 1,12,14,16,18 ---	1,6
A	EP 0 426 463 A (VALIO MEIJERIEN) 8 May 1991 see page 3, line 54 - line 56 see claims 1,9,11 --- -/--	1,6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 1997	14.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Dekeirel, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 01803 A (AGRONOMIQUE INST NAT RECH) 21 February 1991 see page 1, line 12 - line 23 see page 4, line 35 - page 5, line 12 see claims 1,11,27,34-36	1,6
A	EP 0 231 817 A (BUEHLER AG GEB) 12 August 1987 see claims 1,2,4,5	1,6
A	EP 0 707 798 A (CHEVITA GMBH) 24 April 1996 see example 3 see claim 1	1,6
A	EP 0 556 883 A (GIST BROCADES NV) 25 August 1993 see claims 1-5	1,6
A	WO 96 04933 A (WISCONSIN ALUMNI RES FOUND) 22 February 1996 see page 9, line 22 - page 10, line 6 see example 7 see claims 1,28,41-47	1,2,6-8
P,A	WO 96 22028 A (GRAMPIAN PHARM LTD ;LAVERY MARTIN (GB)) 25 July 1996 see page 3, line 31 - line 36 see example 3 see claims 1,6,10	1,6

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/01034

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0241441 A	14-10-87	SE 454230 B	18-04-88
		DE 3775593 A	13-02-92
		SE 8601543 A	08-10-87
		US 4943437 A	24-07-90
WO 9421284 A	29-09-94	AU 673589 B	14-11-96
		AU 6278794 A	11-10-94
		EP 0706400 A	17-04-96
		JP 8509965 T	22-10-96
EP 0426463 A	08-05-91	JP 3169337 A	23-07-91
		US 5104662 A	14-04-92
WO 9101803 A	21-02-91	FR 2650758 A	15-02-91
		EP 0437598 A	24-07-91
EP 0231817 A	12-08-87	CH 666386 A	29-07-88
		DE 3772399 A	07-11-91
EP 0707798 A	24-04-96	NONE	
EP 0556883 A	25-08-93	JP 6505881 T	07-07-94
		WO 9314645 A	05-08-93
		NO 933400 A	17-11-93
WO 9604933 A	22-02-96	AU 3103495 A	07-03-96
		CA 2196594 A	22-02-96
		EP 0769964 A	02-05-97
WO 9622028 A	25-07-96	AU 4395396 A	07-08-96